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(54) Title: IMPROVED ADENOVIRUS AND METHODS OF USE THEREOF (57) Abstract <p>A recombinant adenovirus and a method for producing the virus are provided which utilize a recombinant shuttle vector comprising adenovirus DNA sequence for the 5' and 3' cis-elements necessary for replication and virion encapsidation in the absence of sequence encoding viral genes and a selected minigene linked thereto, and a helper adenovirus comprising sufficient adenovirus gene sequences necessary for a productive viral infection. Desirably the helper gene is crippled by modifications to its 5' packaging sequences, which facilitates purification of the viral particle from the helper virus.</p>		

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IMPROVED ADENOVIRUS AND METHODS OF USE THEREOF

This invention was supported by the National
Institute of Health Grant No. P30 DK 47757. The United
5 States government has rights in this invention.

Field of the Invention

The present invention relates to the field of
vectors useful in somatic gene therapy and the production
10 thereof.

Background of the Invention

Human gene therapy is an approach to treating human
disease that is based on the modification of gene
15 expression in cells of the patient. It has become
apparent over the last decade that the single most
outstanding barrier to the success of gene therapy as a
strategy for treating inherited diseases, cancer, and
other genetic dysfunctions is the development of useful
20 gene transfer vehicles. Eukaryotic viruses have been
employed as vehicles for somatic gene therapy. Among the
viral vectors that have been cited frequently in gene
therapy research are adenoviruses.

Adenoviruses are eukaryotic DNA viruses that can be
25 modified to efficiently deliver a therapeutic or reporter
transgene to a variety of cell types. Recombinant
adenoviruses types 2 and 5 (Ad2 and Ad5, respectively),
which cause respiratory disease in humans, are currently
being developed for gene therapy. Both Ad2 and Ad5
30 belong to a subclass of adenovirus that are not
associated with human malignancies. Recombinant
adenoviruses are capable of providing extremely high
levels of transgene delivery to virtually all cell types,
regardless of the mitotic state. High titers (10^{13}
35 plaque forming units/ml) of recombinant virus can be
easily generated in 293 cells (the adenovirus equivalent

to retrovirus packaging cell lines) and cryo-stored for extended periods without appreciable losses. The efficacy of this system in delivering a therapeutic transgene in vivo that complements a genetic imbalance has been demonstrated in animal models of various disorders [Y. Watanabe, Atherosclerosis, 36:261-268 (1986); K. Tanzawa et al, FEBS Letters, 118(1):81-84 (1980); J.L. Golastan et al, New Engl. J. Med., 309(11983):288-296 (1983); S. Ishibashi et al, J. Clin. Invest., 92:883-893 (1993); and S. Ishibashi et al, J. Clin. Invest., 93:1885-1893 (1994)]. Indeed, a recombinant replication defective adenovirus encoding a cDNA for the cystic fibrosis transmembrane regulator (CFTR) has been approved for use in at least two human clinical trials [see, e.g., J. Wilson, Nature, 365:691-692 (Oct. 21, 1993)]. Further support of the safety of recombinant adenoviruses for gene therapy is the extensive experience of live adenovirus vaccines in human populations.

Human adenoviruses are comprised of a linear, approximately 36 kb double-stranded DNA genome, which is divided into 100 map units (m.u.), each of which is 360 bp in length. The DNA contains short inverted terminal repeats (ITR) at each end of the genome that are required for viral DNA replication. The gene products are organized into early (E1 through E4) and late (L1 through L5) regions, based on expression before or after the initiation of viral DNA synthesis [see, e.g., Horwitz, Virology, 2d edit., ed. B. N. Fields, Raven Press, Ltd., New York (1990)].

The first-generation recombinant, replication-deficient adenoviruses which have been developed for gene therapy contain deletions of the entire E1a and part of the E1b regions. This replication-defective virus is grown on an adenovirus-transformed, complementation human

embryonic kidney cell line containing a functional adenovirus E1a gene which provides a transacting E1a protein, the 293 cell [ATCC CRL1573]. E1-deleted viruses are capable of replicating and producing infectious virus in the 293 cells, which provides E1a and E1b region gene products in trans. The resulting virus is capable of infecting many cell types and can express the introduced gene (providing it carries its own promoter), but cannot replicate in a cell that does not carry the E1 region DNA unless the cell is infected at a very high multiplicity of infection.

However, *in vivo* studies revealed transgene expression in these E1 deleted vectors was transient and invariably associated with the development of severe inflammation at the site of vector targeting [S. Ishibashi et al, J. Clin. Invest., 93:1885-1893 (1994); J. M. Wilson et al, Proc. Natl. Acad. Sci., USA, 85:4421-4424 (1988); J. M. Wilson et al, Clin. Bio., 3:21-26 (1991); M. Grossman et al, Som. Cell. and Mol. Gen., 17:601-607 (1991)]. One explanation that has been proposed to explain this finding is that first generation recombinant adenoviruses, despite the deletion of E1 genes, express low levels of other viral proteins. This could be due to basal expression from the unstimulated viral promoters or transactivation by cellular factors. Expression of viral proteins leads to cellular immune responses to the genetically modified cells, resulting in their destruction and replacement with nontransgene containing cells.

There yet remains a need in the art for the development of additional adenovirus vector constructs for gene therapy.

Summary of the Invention

In one aspect, the invention provides the components of a novel recombinant adenovirus production system. One component is a shuttle plasmid, pAdA, that comprises adenovirus cis-elements necessary for replication and virion encapsidation and is deleted of all viral genes. This vector carries a selected transgene under the control of a selected promoter and other conventional vector/plasmid regulatory components. The other component is a helper adenovirus, which alone or with a packaging cell line, supplies sufficient gene sequences necessary for a productive viral infection. In a preferred embodiment, the helper virus has been altered to contain modifications to the native gene sequences which direct efficient packaging, so as to substantially disable or "cripple" the packaging function of the helper virus or its ability to replicate.

In another aspect, the present invention provides a unique recombinant adenovirus, an AdA virus, produced by use of the components above. This recombinant virus comprises an adenovirus capsid, adenovirus cis-elements necessary for replication and virion encapsidation, but is deleted of all viral genes (i.e., all viral open reading frames). This virus particle carries a selected transgene under the control of a selected promoter and other conventional vector regulatory components. This AdA recombinant virus is characterized by high titer transgene delivery to a host cell and the ability to stably integrate the transgene into the host cell chromosome. In one embodiment, the virus carries as its transgene a reporter gene. Another embodiment of the recombinant virus contains a therapeutic transgene.

In another aspect, the invention provides a method for producing the above-described recombinant AdA virus by co-transfecting a cell line (either a packaging cell

line or a non-packaging cell line) with a shuttle vector or plasmid and a helper adenovirus as described above, wherein the transfected cell generates the AdΔ virus. The AdΔ virus is subsequently isolated and purified therefrom.

In yet a further aspect, the invention provides a method for delivering a selected gene to a host cell for expression in that cell by administering an effective amount of a recombinant AdΔ virus containing a therapeutic transgene to a patient to treat or correct a genetically associated disorder or disease.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

Brief Description of the Figures

Fig. 1A is a schematic representation of the organization of the major functional elements that define the 5' terminus from Ad5 including an inverted terminal repeat (ITR) and a packaging/enhancer domain. The TATA box of the E1 promoter (black box) and E1A transcriptional start site (arrow) are also shown.

Fig. 1B is an expanded schematic of the packaging/enhancer region of Fig. 1A, indicating the five packaging (PAC) domains (A-repeats), I through V. The arrows indicate the location of PCR primers referenced in Figs. 9A and 9B below.

Fig. 2A is a schematic of shuttle vector pAdΔ.CMVlacZ containing 5' ITR from Ad5, followed by a CMV promoter/enhancer, a LacZ gene, a 3' ITR from Ad5, and remaining plasmid sequence from plasmid pSP72 backbone. Restriction endonuclease enzymes are represented by conventional designations in the plasmid constructs.

Fig. 2B is a schematic of the shuttle vector digested with EcoRI to release the modified AdA genome from the pSP72 plasmid backbone.

Fig. 2C is a schematic depiction of the function of the vector system. In the presence of an E1-deleted helper virus Ad.CBhpAP which encodes a reporter minigene for human placenta alkaline phosphatase (hpAP), the AdA.CMVLacZ genome is packaged into preformed virion capsids, distinguishable from the helper virions by the presence of the LacZ gene.

Figs. 3A to 3F [SEQ ID NO: 1] report the top DNA strand of the double-stranded plasmid pAdA.CMVLacZ. The complementary sequence may be readily obtained by one of skill in the art. The sequence includes the following components: 3' Ad ITR (nucleotides 607-28 of SEQ ID NO: 1); the 5' Ad ITR (nucleotides 5496-5144 of SEQ ID NO: 1); CMV promoter/enhancer (nucleotides 5117-4524 of SEQ ID NO: 1); SD/SA sequence (nucleotides 4507-4376 of SEQ ID NO: 1); LacZ gene (nucleotides 4320-845 of SEQ ID NO: 1); and a poly A sequence (nucleotides 837-639 of SEQ ID NO: 1).

Fig. 4A is a schematic of shuttle vector pAdAc.CMVLacZ containing an Ad5 5' ITR and 3' ITR positioned head-to-tail, with a CMV enhancer/promoter-LacZ minigene immediately following the 5' ITR, followed by a plasmid pSP72 (Promega) backbone. Restriction endonuclease enzymes are represented by conventional designations in the plasmid constructs.

Fig. 4B is a schematic depiction of the function of the vector system of Fig. 4A. In the presence of helper virus Ad.CBhpAP, the circular pAdAc.CMVLacZ shuttle vector sequence is packaged into virion heads, distinguishable from the helper virions by the presence of the LacZ gene.

Figs. 5A to 5F [SEQ ID NO: 2] report the top DNA strand of the double-stranded vector pAdΔc.CMVlacZ. The complementary sequence may be readily obtained by one of skill in the art. The sequence includes the following components: 5' Ad ITR (nucleotides 600-958 of SEQ ID NO: 2); CMV promoter/enhancer (nucleotides 969-1563 of SEQ ID NO: 2); SD/SA sequence (nucleotides 1579-1711); LacZ gene (nucleotides 1762-5236 of SEQ ID NO: 2); poly A sequence (nucleotides 5245-5443 of SEQ ID NO: 2); and 3' Ad ITR (nucleotides 16-596 of SEQ ID NO: 2).

Fig. 6 is a schematic of shuttle vector pAdΔ.CBCFTR containing 5' ITR from Ad5, followed by a chimeric CMV enhancer/β actin promoter enhancer, a CFTR gene, a poly-A sequence, a 3' ITR from Ad5, and remaining plasmid sequence from plasmid pSL1180 (Pharmacia) backbone. Restriction endonuclease enzymes are represented by conventional designations in the plasmid constructs.

Figs. 7A to 7H [SEQ ID NO: 3] report the top DNA strand of the double-stranded plasmid pAdΔ.CBCFTR. The complementary sequence may be readily obtained by one of skill in the art. The sequence includes the following components: 5' Ad ITR (nucleotides 9611-9254 of SEQ ID NO: 3); chimeric CMV enhancer/β actin promoter (nucleotides 9241-8684 of SEQ ID NO: 3); CFTR gene (nucleotides 8622-4065 of SEQ ID NO: 3); poly A sequence (nucleotides 3887-3684 of SEQ ID NO: 3); and 3' Ad ITR (nucleotides 3652-3073 of SEQ ID NO: 3). The remaining plasmid backbone is obtained from pSL1180 (Pharmacia).

Fig. 8A illustrates the generation of 5' adenovirus terminal sequence that contained PAC domains I and II by PCR. See, arrows indicating righthand and lefthand (PAC II) PCR probes in Fig. 1B.

Fig. 8B illustrates the generation of 5' terminal sequence that contained PAC domains I, II, III and IV by PCR. See, arrows indicating righthand and lefthand (PAC IV) PCR probes in Fig. 1B.

5 Fig. 8C depicts the amplification products subcloned into the multiple cloning site of pAd.Link.1 (IHGT Vector Core) generating pAd.PACII (domains I and II) and pAd.PACIV (domains I, II, III, and IV) resulting in crippled helper viruses, Ad.PACII and Ad.PACIV with
10 modified packaging (PAC) signals.

Fig. 9A is a schematic representation of the subcloning of a human placenta alkaline phosphatase reporter minigene containing the immediate early CMV enhancer/ promoter (CMV), human placenta alkaline
15 phosphatase cDNA (hpAP), and SV40 polyadenylation signal (pA) into pAd.PACII to result in crippled helper virus vector pAdΔ.PACII.CMVhpAP. Restriction endonuclease enzymes are represented by conventional designations in the plasmid constructs.

20 Fig. 9B is a schematic representation of the subcloning of the same minigene of Fig. 9A into pAd.PACIV to result in crippled helper virus vector pAd.PACIV.CMV.hpAP.

Fig. 10 is a flow diagram summarizing the synthesis
25 of an adenovirus-based polycation helper virus conjugate and its combination with a pAdΔ shuttle vector to result in a novel viral particle complex. CsCl band purified helper adenovirus was reacted with the heterobifunctional crosslinker sulfo-SMCC and the capsid protein fiber is
30 labeled with the nucleophilic maleimide moiety. Free sulfhydryls were introduced onto poly-L-lysine using 2-iminothiolane-HCl and mixed with the labelled adenovirus, resulting in the helper virus conjugate Ad-pLys. A unique adenovirus-based particle is generated by
35 purifying the Ad-pLys conjugate over a CsCl gradient to

remove unincorporated poly-L-lysine, followed by extensively dialyzing, adding shuttle plasmid DNAs to Ad-pLys and allowing the complex formed by the shuttle plasmid wrapped around Ad-pLys to develop.

5 Fig. 11 is a schematic diagram of pCCL-DMD, which is described in detail in Example 9 below.

Fig. 12A - 12P provides the continuous DNA sequence of pAdΔ.CMVmDys [SEQ ID NO:10].

10 Detailed Description of the Invention

The present invention provides a unique recombinant adenovirus capable of delivering transgenes to target cells, as well as the components for production of the unique virus and methods for the use of the virus to
15 treat a variety of genetic disorders.

The AdΔ virus of this invention is a viral particle containing only the adenovirus cis-elements necessary for replication and virion encapsidation (i.e., ITRs and packaging sequences), but otherwise deleted of all
20 adenovirus genes (i.e., all viral open reading frames). This virus carries a selected transgene under the control of a selected promoter and other conventional regulatory components, such as a poly A signal. The AdΔ virus is characterized by improved persistence of the vector DNA
25 in the host cells, reduced antigenicity/immunogenicity, and hence, improved performance as a delivery vehicle. An additional advantage of this invention is that the AdΔ virus permits the packaging of very large transgenes, such as a full-length dystrophin cDNA for the treatment
30 of the progressive wasting of muscle tissue characteristic of Duchenne Muscular Dystrophy (DMD).

This novel recombinant virus is produced by use of an adenovirus-based vector production system containing two components: 1) a shuttle vector that comprises
35 adenovirus cis-elements necessary for replication and

virion encapsidation and is deleted of all viral genes, which vector carries a reporter or therapeutic minigene and 2) a helper adenovirus which, alone or with a packaging cell line, is capable of providing all of the viral gene products necessary for a productive viral infection when co-transfected with the shuttle vector. Preferably, the helper virus is modified so that it does not package itself efficiently. In this setting, it is desirably used in combination with a packaging cell line that stably expresses adenovirus genes. The methods of producing this viral vector from these components include both a novel means of packaging of an adenoviral/transgene containing vector into a virus, and a novel method for the subsequent separation of the helper virus from the newly formed recombinant virus.

I. The Shuttle Vector

The shuttle vector, referred to as pAdΔ, is composed of adenovirus sequences, and transgene sequences, including vector regulatory control sequences.

A. The Adenovirus Sequences

The adenovirus nucleic acid sequences of the shuttle vector provide the minimum adenovirus sequences which enable a viral particle to be produced with the assistance of a helper virus. These sequences assist in delivery of a recombinant transgene genome to a target cell by the resulting recombinant virus.

The DNA sequences of a number of adenovirus types are available from Genbank, including type Ad5 [Genbank Accession No. M73260]. The adenovirus sequences may be obtained from any known adenovirus serotype, such as serotypes 2, 3, 4, 7, 12 and 40, and further including any of the presently identified 41 human types [see, e.g., Horwitz, cited above]. Similarly adenoviruses known to infect other animals may also be employed in the

vector constructs of this invention. The selection of the adenovirus type is not anticipated to limit the following invention. A variety of adenovirus strains are available from the American Type Culture Collection, 5 Rockville, Maryland, or available by request from a variety of commercial and institutional sources. In the following exemplary embodiment an adenovirus, type 5 (Ad5) is used for convenience.

However, it is desirable to obtain a variety of 10 pAdΔ shuttle vectors based on different human adenovirus serotypes. It is anticipated that a library of such plasmids and the resulting AdΔ viral vectors would be useful in a therapeutic regimen to evade cellular, and possibly humoral, immunity, and lengthen the duration of 15 transgene expression, as well as improve the success of repeat therapeutic treatments. Additionally the use of various serotypes is believed to produce recombinant viruses with different tissue targeting specificities. The absence of adenoviral genes in the AdΔ viral vector 20 is anticipated to reduce or eliminate adverse CTL response which normally causes destruction of recombinant adenoviruses deleted of only the E1 gene.

Specifically, the adenovirus nucleic acid sequences employed in the pAdΔ shuttle vector of this 25 invention are adenovirus genomic sequences from which all viral genes are deleted. More specifically, the adenovirus sequences employed are the cis-acting 5' and 3' inverted terminal repeat (ITR) sequences of an adenovirus (which function as origins of replication) and 30 the native 5' packaging/enhancer domain, that contains sequences necessary for packaging linear Ad genomes and enhancer elements for the E1 promoter. These sequences are the sequences necessary for replication and virion encapsidation. See, e.g., P. Hearing et al, J. Virol., 35 61(8):2555-2558 (1987); M. Grable and P. Hearing, J.

Virology, 64(5): 2047-2056 (1990); and M. Grable and P. Hearing, J. Virology, 66(2):723-731 (1992).

According to this invention, the entire adenovirus 5' sequence containing the 5' ITR and packaging/enhancer region can be employed as the 5' adenovirus sequence in the pAdΔ shuttle vector. This left terminal (5') sequence of the Ad5 genome useful in this invention spans bp 1 to about 360 of the conventional adenovirus genome, also referred to as map units 0-1 of the viral genome. This sequence is provided herein as nucleotides 5496-5144 of SEQ ID NO: 1, nucleotides 600-958 of SEQ ID NO: 2; and nucleotides 9611-9254 of SEQ ID NO: 3, and generally is from about 353 to about 360 nucleotides in length. This sequence includes the 5' ITR (bp 1-103 of the adenovirus genome), and the packaging/enhancer domain (bp 194-358 of the adenovirus genome). See, Figs. 1A, 3, 5, and 7.

Preferably, this native adenovirus 5' region is employed in the shuttle vector in unmodified form. However, some modifications including deletions, substitutions and additions to this sequence which do not adversely effect its biological function may be acceptable. See, e.g., WO 93/24641, published December 9, 1993. The ability to modify these ITR sequences is within the ability of one of skill in the art. See, e.g., texts such as Sambrook et al, "Molecular Cloning. A Laboratory Manual.", 2d edit., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York (1989).

The 3' adenovirus sequences of the shuttle vector include the right terminal (3') ITR sequence of the adenoviral genome spanning about bp 35,353 - end of the adenovirus genome, or map units -98.4-100. This sequence is provided herein as nucleotides 607-28 of SEQ ID NO: 1, nucleotides 16-596 of SEQ ID NO: 2; and nucleotides 3652-3073 of SEQ ID NO: 3, and generally is

about 580 nucleotides in length. This entire sequence is desirably employed as the 3' sequence of an pAdA shuttle vector. Preferably, the native adenovirus 3' region is employed in the shuttle vector in unmodified form.

5 However, some modifications to this sequence which do not adversely effect its biological function may be acceptable.

An exemplary pAdA shuttle vector of this invention, described below and in Fig. 2A, contains only
10 those adenovirus sequences required for packaging adenoviral genomic DNA into a preformed capsid head. The pAdA vector contains Ad5 sequences encoding the 5' terminal and 3' terminal sequences (identified in the description of Fig. 3), as well as the transgene
15 sequences described below.

From the foregoing information, it is expected that one of skill in the art may employ other equivalent adenovirus sequences for use in the AdA vectors of this invention. These sequences may include other adenovirus
20 strains, or the above mentioned cis-acting sequences with minor modifications.

B. The Transgene

The transgene sequence of the vector and recombinant virus is a nucleic acid sequence or reverse
25 transcript thereof, heterologous to the adenovirus sequence, which encodes a polypeptide or protein of interest. The transgene is operatively linked to regulatory components in a manner which permits transgene transcription.

30 The composition of the transgene sequence will depend upon the use to which the resulting virus will be put. For example, one type of transgene sequence includes a reporter sequence, which upon expression produces a detectable signal. Such reporter sequences
35 include without limitation an *E. coli* beta-galactosidase

(LacZ) cDNA, a human placental alkaline phosphatase gene and a green fluorescent protein gene. These sequences, when associated with regulatory elements which drive their expression, provide signals detectable by conventional means, e.g., ultraviolet wavelength absorbance, visible color change, etc.

Another type of transgene sequence includes a therapeutic gene which expresses a desired gene product in a host cell. These therapeutic nucleic acid sequences typically encode products for administration and expression in a patient in vivo or ex vivo to replace or correct an inherited or non-inherited genetic defect or treat an epigenetic disorder or disease. Such therapeutic genes which are desirable for the performance of gene therapy include, without limitation, a normal cystic fibrosis transmembrane regulator (CFTR) gene (see Fig. 7), a low density lipoprotein (LDL) gene [T. Yamamoto et al, *Cell*, 39:27-28 (November, 1984)], a DMD cDNA sequence [partial sequences available from GenBank, Accession Nos. M36673, M36671, [A. P. Monaco et al, *Nature*, 323:646-650 (1986)] and L06900, [Roberts et al, *Hum. Mutat.*, 2:293-299 (1993)]] (Genbank), and a number of genes which may be readily selected by one of skill in the art. The selection of the transgene is not considered to be a limitation of this invention, as such selection is within the knowledge of the art-skilled.

C. Regulatory Elements

In addition to the major elements identified above for the pAdA shuttle vector, i.e., the adenovirus sequences and the transgene, the vector also includes conventional regulatory elements necessary to drive expression of the transgene in a cell transfected with the pAdA vector. Thus the vector contains a selected promoter which is linked to the transgene and located,

with the transgene, between the adenovirus sequences of the vector.

Selection of the promoter is a routine matter and is not a limitation of the pAdA vector itself.

5 Useful promoters may be constitutive promoters or regulated (inducible) promoters, which will enable control of the amount of the transgene to be expressed. For example, a desirable promoter is that of the cytomegalovirus immediate early promoter/enhancer [see,
10 e.g., Boshart et al, Cell, 41:521-530 (1985)]. This promoter is found at nucleotides 5117-4524 of SEQ ID NO: 1 and nucleotides 969-1563 of SEQ ID NO: 2. Another promoter is the CMV enhancer/chicken B-actin promoter (nucleotides 9241-8684 of SEQ ID NO: 3). Another
15 desirable promoter includes, without limitation, the Rous sarcoma virus LTR promoter/enhancer. Still other promoter/enhancer sequences may be selected by one of skill in the art.

The shuttle vectors will also desirably contain
20 nucleic acid sequences heterologous to the adenovirus sequences including sequences providing signals required for efficient polyadenylation of the transcript and introns with functional splice donor and acceptor sites (SD/SA). A common poly-A sequence which is employed in
25 the exemplary vectors of this invention is that derived from the papovavirus SV-40 [see, e.g., nucleotides 837-639 of SEQ ID NO: 1; 5245-5443 of SEQ ID NO: 2; and 3887-3684 of SEQ ID NO: 3]. The poly-A sequence generally is inserted in the vector following the transgene sequences
30 and before the 3' adenovirus sequences. A common intron sequence is also derived from SV-40, and is referred to as the SV-40 T intron sequence [see, e.g., nucleotides 4507-4376 of SEQ ID NO: 1 and 1579-1711 of SEQ ID NO: 2]. A pAdA shuttle vector of the present invention may also
35 contain such an intron, desirably located between the

promoter/enhancer sequence and the transgene. Selection of these and other common vector elements are conventional and many such sequences are available [see, e.g., Sambrook et al, and references cited therein].

- 5 Examples of such regulatory sequences for the above are provided in the plasmid sequences of Figs. 3, 5 and 7.

The combination of the transgene, promoter/enhancer, the other regulatory vector elements are referred to as a "minigene" for ease of reference herein.

- 10 The minigene is preferably flanked by the 5' and 3' cis-acting adenovirus sequences described above. Such a minigene may have a size in the range of several hundred base pairs up to about 30 kb due to the absence of adenovirus early and late gene sequences in the vector.
- 15 Thus, this AdA vector system permits a great deal of latitude in the selection of the various components of the minigene, particularly the selected transgene, with regard to size. Provided with the teachings of this invention, the design of such a minigene can be made by
- 20 resort to conventional techniques.

II. The Helper Virus

- Because of the limited amount of adenovirus sequence present in the AdA shuttle vector, a helper adenovirus of
- 25 this invention must, alone or in concert with a packaging cell line, provide sufficient adenovirus gene sequences necessary for a productive viral infection. Helper viruses useful in this invention thus contain selected adenovirus gene sequences, and optionally a second
- 30 reporter minigene.

- Normally, the production of a recombinant adenovirus which utilizes helper adenovirus containing a full complement of adenoviral genes results in recombinant virus contaminated by excess production of the helper
- 35 virus. Thus, extensive purification of the viral vector

from the contaminating helper virus is required. However, the present invention provides a way to facilitate purification and reduce contamination by crippling the helper virus.

5 One preferred embodiment of a helper virus of this invention thus contains three components (A) modifications or deletions of the native adenoviral gene sequences which direct efficient packaging, so as to substantially disable or "cripple" the packaging function
10 of the helper virus or its ability to replicate, (B) selected adenovirus genes and (C) an optional reporter minigene. These "crippled" helper viruses may also be formed into poly-cation conjugates as described below.

The adenovirus sequences forming the helper virus
15 may be obtained from the sources identified above in the discussion of the shuttle vector. Use of different Ad serotypes as helper viruses enables production of recombinant viruses containing the Δ Ad (serotype 5) shuttle vector sequences in a capsid formed by the other
20 serotype adenovirus. These recombinant viruses are desirable in targeting different tissues, or evading an immune response to the Δ Ad sequences having a serotype 5 capsid. Use of these different Ad serotype helper
25 viruses may also demonstrate advantages in recombinant virus production, stability and better packaging.

A. The Crippling Modifications

A desirable helper virus used in the production of the adenovirus vector of this invention is modified (or crippled) in its 5' ITR packaging/enhancer domain,
30 identified above. As stated above, the packaging/enhancer region contains sequences necessary for packaging linear adenovirus genomes ("PAC" sequences). More specifically, this sequence contains at least seven distinct yet functionally redundant domains

that are required for efficient encapsidation of replicated viral DNA.

Within a stretch of nucleotide sequence from bp 194-358 of the Ad5 genome, five of these so-called A-repeats or PAC sequences are localized (see, Fig. 1B). PAC I is located at bp 241-248 of the adenovirus genome (on the strand complementary to nucleotides 5259-5246 of SEQ ID NO: 1). PAC II is located at bp 262-269 of the adenovirus genome (on the strand complementary to nucleotides 5238-5225 of SEQ ID NO: 1). PAC III is located at bp 304-311 of the adenovirus genome (on the strand complementary to nucleotides 5196-5183 of SEQ ID NO: 1). PAC IV is located at bp 314-321 of the adenovirus (on the strand complementary to nucleotides 5186-5172 of SEQ ID NO: 1). PAC V is located at bp 339-346 of the adenovirus (on the strand complementary to nucleotides 5171-5147 of SEQ ID NO: 1).

Corresponding sequences can be obtained from SEQ ID NO: 2 and 3. PAC I is located at nucleotides 837-851 of SEQ ID NO: 2; and on the strand complementary to nucleotides 9374-9360 of SEQ ID NO: 3. PAC II is located at nucleotides 859-863 of SEQ ID NO: 2; and on the strand complementary to nucleotides 9353-9340 of SEQ ID NO: 3. PAC III is located at nucleotides 901-916 of SEQ ID NO: 2; and on the strand complementary to nucleotides 9311-9298 of SEQ ID NO: 3. PAC IV is located at nucleotides 911-924 of SEQ ID NO: 2; and on the strand complementary to nucleotides 9301-9288 of SEQ ID NO: 3. PAC V is located at nucleotides 936-949 of SEQ ID NO: 2; and on the strand complementary to nucleotides 9276-9263 of SEQ ID NO: 3.

Table 1 below lists these five native Ad5 sequences and a consensus PAC sequence based on the similarities between an eight nucleic acid stretch within the five sequences. The consensus sequence contains two positions at which the nucleic acid may be A or T (A/T). The conventional single letter designations are used for the nucleic acids, as is known to the art.

Table 1	
<u>A-Repeat</u>	<u>Adenovirus Genome Base Pair Nos. & Nucleotide sequence</u>
I	241 248 TAG TAAATTTG GGC [SEQ ID NO: 4]
II	262 269 AGT AAGATTTG GCC [SEQ ID NO: 5]
III	304 311 AGT GAAATCTG AAT [SEQ ID NO: 6]
IV	314 321 GAA TAATTTTG TGT [SEQ ID NO: 7]
V	339 346 CGT AATATTTG TCT [SEQ ID NO: 8]
Consensus	5' (A/T)AN(A/T)TTTG 3' [SEQ ID NO: 9]

According to this invention, mutations or deletions may be made to one or more of these PAC sequences to generate desirable crippled helper viruses. A deletion analysis of the packaging domain revealed a positive correlation between encapsidation efficiency and the number of packaging A-repeats that were present at the 5' end of the genome. Modifications of this domain may include 5' adenovirus sequences which contain less than all five of the PAC sequences of Table 1. For example, only two PAC sequences may be present in the crippled virus, e.g., PAC I and PAC II, PAC III and PAC IV, and so on. Deletions of selected PAC sequences may

involve deletion of contiguous or non-contiguous sequences. For example, PAC II and PAC IV may be deleted, leaving PAC I, III and IV in the 5' sequence. Still an alternative modification may be the replacement
5 of one or more of the native PAC sequences with one or more repeats of the consensus sequence of Table 1. Alternatively, this adenovirus region may be modified by deliberately inserted mutations which disrupt one or more of the native PAC sequences. One of skill in the art may
10 further manipulate the PAC sequences to similarly achieve the effect of reducing the helper virus packaging efficiency to a desired level.

Exemplary helper viruses which involve the manipulation of the PAC sequences described above are
15 disclosed in Example 7 below. Briefly, as described in that example, one helper virus contains in place of the native 5' ITR region (adenovirus genome bp 1-360), a 5' adenovirus sequence spanning adenovirus genome bp 1-269, which contains only the 5' ITR and PAC I and PAC II
20 sequences, and deletes the adenovirus region bp 270-360.

Another PAC sequence modified helper virus contains only the 5' Ad5 sequence of the ITR and PAC I through PAC IV (Ad bp 1-321), deleting PAC V and other sequences in the Ad region bp 322-360.

25 These modified helper viruses are characterized by reduced efficiency of helper virus encapsidation. These helper viruses with the specific modifications of the sequences related to packaging efficiency, provide a packaging efficiency high enough for generating
30 production lots of the helper virus, yet low enough that they permit the achievement of higher yields of AdA transducing viral particles according to this invention.

B. The Selected Adenovirus Genes

Helper viruses useful in this invention, whether or not they contain the "crippling" modifications described above, contain selected adenovirus gene sequences depending upon the cell line which is transfected by the helper virus and shuttle vector. A preferred helper virus contains a variety of adenovirus genes in addition to the modified sequences described above.

As one example, if the cell line employed to produce the recombinant virus is not a packaging cell line, the helper virus may be a wild type Ad virus. Thus, the helper virus supplies the necessary adenovirus early genes E1, E2, E4 and all remaining late, intermediate, structural and non-structural genes of the adenovirus genome. This helper virus may be a crippled helper virus by incorporating modifications in its native 5' packaging/enhancer domain.

A desirable helper virus is replication defective and lacks all or a sufficient portion of the adenoviral early immediate early gene E1a (which spans mu 1.3 to 4.5) and delayed early gene E1b (which spans mu 4.6 to 11.2) so as to eliminate their normal biological functions. Such replication deficient viruses may also have crippling modifications in the packaging/enhancer domain. Because of the difficulty surrounding the absolute removal of adenovirus from AdA preparations that have been enriched by CsCl buoyant density centrifugation, the use of a replication defective adenovirus helper prevents the introduction of infectious adenovirus for *in vivo* animal studies. This helper virus is employed with a packaging cell line which supplies the deficient E1 proteins, such as the 293 cell line.

Additionally, all or a portion of the adenovirus delayed early gene E3 (which spans mu 76.6 to 86.2) may be eliminated from the adenovirus sequence which forms a part of the helper viruses useful in this invention, without adversely affecting the function of the helper virus because this gene product is not necessary for the formation of a functioning virus.

In the presence of other packaging cell lines which are capable of supplying adenoviral proteins in addition to the E1, the helper virus may accordingly be deleted of the genes encoding these adenoviral proteins. Such additionally deleted helper viruses also desirably contain crippling modifications as described above.

C. A Reporter Minigene

It is also desirable for the helper virus to contain a reporter minigene, in which the reporter gene is desirably different from the reporter transgene contained in the shuttle vector. A number of such reporter genes are known, as referred to above. The presence of a reporter gene on the helper virus which is different from the reporter gene on the pAdA, allows both the recombinant AdA virus and the helper virus to be independently monitored. For example, the expression of recombinant alkaline phosphatase enables residual quantities of contaminating adenovirus to be monitored independent of recombinant LacZ expressed by an pAdA shuttle vector or an AdA virus.

D. Helper Virus Polycation Conjugates

Still another method for reducing the contamination of helper virus involves the formation of poly-cation helper virus conjugates, which may be associated with a plasmid containing other adenoviral genes, which are not present in the helper virus. The helper viruses described above may be further modified by resort to adenovirus-polylysine conjugate technology.

See, e.g., Wu et al, J. Biol. Chem., 264:16985-16987 (1989); and K. J. Fisher and J. M. Wilson, Biochem. J., 299: 49 (April 1, 1994), incorporated herein by reference.

5 Using this technology, a helper virus containing preferably the late adenoviral genes is modified by the addition of a poly-cation sequence distributed around the capsid of the helper virus. Preferably, the poly-cation is poly-lysine, which
10 attaches around the negatively-charged vector to form an external positive charge. A plasmid is then designed to express those adenoviral genes not present in the helper virus, e.g., the E1, E2 and/or E4 genes. The plasmid associates to the helper virus-conjugate through the
15 charges on the poly-lysine sequence. This modification is also desirably made to a crippled helper virus of this invention. This conjugate (also termed a trans-infection particle) permits additional adenovirus genes to be removed from the helper virus and be present on a plasmid
20 which does not become incorporated into the virus during production of the recombinant viral vector. Thus, the impact of contamination is considerably lessened.

25 III. Assembly of Shuttle Vector, Helper Virus and Production of Recombinant Virus

 The material from which the sequences used in the pAdΔ shuttle vector and the helper viruses are derived, as well as the various vector components and sequences employed in the construction of the shuttle vectors,
30 helper viruses, and AdΔ viruses of this invention, are obtained from commercial or academic sources based on previously published and described materials. These materials may also be obtained from an individual patient or generated and selected using standard recombinant
35 molecular cloning techniques known and practiced by those

skilled in the art. Any modification of existing nucleic acid sequences forming the vectors and viruses, including sequence deletions, insertions, and other mutations are also generated using standard techniques.

5 Assembly of the selected DNA sequences of the adenovirus, and the reporter genes or therapeutic genes and other vector elements into the pAdΔ shuttle vector using conventional techniques is described in Example 1 below. Such techniques include conventional cloning
10 techniques of cDNA such as those described in texts [Sambrook et al, cited above], use of overlapping oligonucleotide sequences of the adenovirus genomes, polymerase chain reaction, and any suitable method which provides the desired nucleotide sequence. Standard
15 transfection and co-transfection techniques are employed, e.g., CaPO₄ transfection techniques using the HEK 293 cell line. Other conventional methods employed in this invention include homologous recombination of the viral
20 genomes, plaquing of viruses in agar overlay, methods of measuring signal generation, and the like. Assembly of any desired AdΔ vector or helper virus of this invention is within the skill of the art, based on the teachings of this invention.

A. Shuttle Vector

25 As described in detail in Example 1 below and with resort to Fig. 2A and the DNA sequence of the plasmid reported in Fig. 3, a unique pAdΔ shuttle vector of this invention, pAdΔ.CMVlacZ, is generated.
30 pAdΔ.CMVlacZ contains Ad5 sequences encoding the 5' terminal followed by a CMV promoter/enhancer, a splice donor/splice acceptor sequence, a bacterial beta-galactosidase gene (LacZ), a SV-40 poly A sequence (pA), a 3' ITR from Ad5 and remaining plasmid sequence from plasmid pSP72 (Promega) backbone.

To generate the AdA genome which is incorporated in the vector, the plasmid pAdA.CMVLacZ must be must be digested with EcoRI to release the AdA.CMVLacZ genome, freeing the adenovirus ITRs and making them
5 available targets for replication. Thus production of the vector is "restriction-dependent", i.e., requires restriction endonuclease rescue of the replication template. See, Fig. 2B.

A second type of pAdA plasmid was designed
10 which places the 3' Ad terminal sequence in a head-to-tail arrangement relative to the 5' terminal sequence. As described in Example 1 and Figs. 4A, and with resort to the DNA sequence of the plasmid reported in Fig. 5, a second unique AdA vector sequence of this invention,
15 AdAc.CMVLacZ, is generated from the shuttle plasmid pAdAc.CMVLacZ, which contains an Ad5 5' ITR sequence and 3' ITR sequence positioned head-to-tail, followed by a CMV enhancer/ promoter, SD/SA sequence, LacZ gene and pA sequence in a plasmid pSP72 (Promega) backbone. As
20 described in Example 1B, this "restriction-independent" plasmid permits the AdA genome to be replicated and rescued from the plasmid backbone without including an endonuclease treatment (see, Fig. 4B).

B. Helper Virus

25 As described in detail in Example 2, an exemplary conventional E1 deleted adenovirus helper virus is virus Ad.CBhpAP, which contains a 5' adenovirus sequence from mu 0-1, a reporter minigene containing human placenta alkaline phosphatase (hpAP) under the
30 transcriptional control of the chicken β -actin promoter, followed by a poly-A sequence from SV40, followed by adenovirus sequences from 9.2 to 78.4 and 86 to 100. This helper contained deletions from mu 1.0 to 9.2 and 78.4 to 86, which eliminate substantially the E1 region
35 and the E3 region of the virus. This virus may be

desirably crippled according to this invention by modifications to its packaging enhancer domain.

Exemplary crippled helper viruses of this invention are described using the techniques described in Example 7 and contain the modified 5' PAC sequences, i.e., adenovirus genome bp 1-269; m.u. 0-0.75 or adenovirus genome bp 1-321; m.u. 0-0.89. Briefly, the 5' sequences are modified by PCR and cloned by conventional techniques into a conventional adenovirus based plasmid. A hpAP minigene is incorporated into the plasmid, which is then altered by homologous recombination with an E3 deleted adenovirus dl7001 to result in the modified vectors so that the reporter minigene is followed on its 3' end with the adenovirus sequences mu 9.6 to 78.3 and 87 to 100.

Generation of a poly-L-lysine conjugate helper virus was demonstrated essentially as described in detail in Example 5 below and Fig. 10 by coupling poly-L-lysine to the Ad.CBhpAP virion capsid. Alternatively, the same procedure may be employed with the PAC sequence modified helper viruses of this invention.

C. Recombinant AdA Virus

As stated above, a pAdA shuttle vector in the presence of helper virus and/or a packaging cell line permits the adenovirus-transgene sequences in the shuttle vector to be replicated and packaged into virion capsids, resulting in the recombinant AdA virus. The current method for producing such AdA virus is transfection-based and described in detail in Example 3. Briefly, helper virus is used to infect cells, such as the packaging cell line human HEK 293, which are then subsequently transfected with an pAdA shuttle vector containing a selected transgene by conventional methods. About 30 or more hours post-transfection, the cells are harvested, and an extract prepared. The AdA viral genome is

packaged into virions that sediment at a lower density than the helper virus in cesium gradients. Thus, the recombinant AdA virus containing a selected transgene is separated from the bulk of the helper virus by
5 purification via buoyant density ultracentrifugation in a CsCl gradient.

The yield of AdA transducing virus is largely dependent on the number of cells that are transfected with the pAdA shuttle plasmid, making it desirable to use
10 a transfection protocol with high efficiency. One such method involves use of a poly-L-lysinyated helper adenovirus as described above. A pAdA shuttle plasmid containing the desired transgene under the control of a suitable promoter, as described above, is then complexed
15 directly to the positively charged helper virus capsid, resulting in the formation of a single transfection particle containing the pAdA shuttle vector and the helper functions of the helper virus.

The underlying principle is that the helper
20 adenovirus coated with plasmid pAdA DNA will co-transport the attached nucleic acid across the cell membrane and into the cytoplasm according to its normal mechanism of cell entry. Therefore, the poly-L-lysine modified helper adenovirus assumes multiple roles in the context of an
25 AdA-based complex. First, it is the structural foundation upon which plasmid DNA can bind increasing the effective concentration. Second, receptor mediated endocytosis of the virus provides the vehicle for cell uptake of the plasmid DNA. Third, the endosomalytic
30 activity associated with adenoviral infection facilitates the release of internalized plasmid into the cytoplasm. And the adenovirus contributes trans helper functions on which the recombinant AdA virus is dependent for replication and packaging of transducing viral particles.
35 The Ad-based transfection procedure using an pAdA shuttle

vector and a polycation-helper conjugate is detailed in Example 6. Additionally, as described previously, the helper virus-plasmid conjugate may be another form of helper virus delivery of the omitted adenovirus genes not present in the pAdA vector. Such a structure enables the rest of the required adenovirus genes to be divided between the plasmid and the helper virus, thus reducing the self-replication efficiency of the helper virus.

A presently preferred method of producing the recombinant AdA virus of this invention involves performing the above-described transfection with the crippled helper virus or crippled helper virus conjugate, as described above. A "crippled" helper virus of this invention is unable to package itself efficiently, and therefor permits ready separation of the helper virus from the newly packaged AdA vector of this invention by use of buoyant density ultracentrifugation in a CsCl gradient, as described in the examples below.

IV. Function of the Recombinant AdA Virus

Once the AdA virus of this invention is produced by cooperation of the shuttle vector and helper virus, the AdA virus can be targeted to, and taken up by, a selected target cell. The selection of the target cell also depends upon the use of the recombinant virus, i.e., whether or not the transgene is to be replicated in vitro or ex vivo for production in a desired cell type for redelivery into a patient, or in vivo for delivery to a particular cell type or tissue. Target cells may be any mammalian cell (preferably a human cell). For example, in in vivo use, the recombinant virus can target to any cell type normally infected by adenovirus, depending upon the route of administration, i.e., it can target, without limitation, neurons, hepatocytes, epithelial cells and

the like. The helper adenovirus sequences supply the sequences necessary to permit uptake of the virus by the AdA.

Once the recombinant virus is taken up by a cell,
5 the adenovirus flanked transgene is rescued from the parental adenovirus backbone by the machinery of the infected cell, as with other recombinant adenoviruses. Once uncoupled (rescued) from the genome of the AdA virus, the recombinant minigene seeks an integration site
10 in the host chromatin and becomes integrated therein, either transiently or stably, providing expression of the accompanying transgene in the host cell.

V. Use of the AdA Viruses in Gene Therapy

15 The novel recombinant viruses and viral conjugates of this invention provide efficient gene transfer vehicles for somatic gene therapy. These viruses are prepared to contain a therapeutic gene in place of the LacZ reporter transgene illustrated in the exemplary
20 viruses and vectors. By use of the AdA viruses containing therapeutic transgenes, these transgenes can be delivered to a patient *in vivo* or *ex vivo* to provide for integration of the desired gene into a target cell. Thus, these viruses can be employed to correct genetic
25 deficiencies or defects. An example of the generation of an AdA gene transfer vehicle for the treatment of cystic fibrosis is described in Example 4 below. One of skill in the art can generate any number of other gene transfer vehicles by including a selected transgene for the
30 treatment of other disorders.

The recombinant viruses of the present invention may be administered to a patient, preferably suspended in a biologically compatible solution or pharmaceutically acceptable delivery vehicle. A suitable vehicle includes
35 sterile saline. Other aqueous and non-aqueous isotonic

sterile injection solutions and aqueous and non-aqueous sterile suspensions known to be pharmaceutically acceptable carriers and well known to those of skill in the art may be employed for this purpose.

5 The recombinant viruses of this invention may be administered in sufficient amounts to transfect the desired cells and provide sufficient levels of integration and expression of the selected transgene to provide a therapeutic benefit without undue adverse
10 effects or with medically acceptable physiological effects which can be determined by those skilled in the medical arts. Conventional and pharmaceutically acceptable parenteral routes of administration include
15 direct delivery to the target organ, tissue or site, intranasal, intravenous, intramuscular, subcutaneous, intradermal and oral administration. Routes of administration may be combined, if desired.

 Dosages of the recombinant virus will depend primarily on factors such as the condition being treated,
20 the selected gene, the age, weight and health of the patient, and may thus vary among patients. A therapeutically effective human dosage of the viruses of the present invention is believed to be in the range of
25 from about 20 to about 50 ml of saline solution containing concentrations of from about 1×10^7 to 1×10^{10} pfu/ml virus of the present invention. A preferred human dosage is about 20 ml saline solution at the above concentrations. The dosage will be adjusted to balance
30 the therapeutic benefit against any side effects. The levels of expression of the selected gene can be monitored to determine the selection, adjustment or frequency of dosage administration.

The following examples illustrate the construction of the pAdA shuttle vectors, helper viruses and recombinant AdA viruses of the present invention and the use thereof in gene therapy. These examples are illustrative only, and do not limit the scope of the present invention.

Example 1 - Production of pAdA.CMVLacZ and pAdAc.CMVLacZ Shuttle Vectors

10 A. pAdA.CMVLacZ

A human adenovirus Ad5 sequence was modified to contain a deletion in the E1a region [map units 1 to 9.2], which immediately follows the Ad 5' region (bp 1-360) (illustrated in Figs. 1A). Thus, the plasmid contains the 5' ITR sequence (bp 1-103), the native packaging/enhancer sequences and the TATA box for the E1a region (bp 104-360). A minigene containing the CMV immediate early enhancer/promoter, an SD/SA sequence, a cytoplasmic lacZ gene, and SV40 poly A (pA), was introduced at the site of the E1a deletion. This construct was further modified so that the minigene is followed by the 3' ITR sequences (bp 35,353-end). The DNA sequences for these components are provided in Fig. 3 and SEQ ID NO: 1 (see, also the brief description of this figure).

This construct was then cloned by conventional techniques into a pSP72 vector (Promega) backbone to make the circular shuttle vector pAdACMVLacZ. See the schematic of Fig. 2A. This construct was engineered with EcoRI sites flanking the 5' and 3' Ad5 ITR sequences. pAdA.CMVLacZ was then subjected to enzymatic digestion with EcoRI, releasing a linear fragment of the vector spanning the terminal end of the Ad 5' ITR sequence through the terminal end of the 3' ITR sequence from the plasmid backbone. See Fig. 2B.

B. pAdAc.CMVLacZ

The shuttle vector pAdAc.CMVLacZ (Figs. 4A and 5) was constructed using a pSP72 (Promega) backbone so that the Ad5 5' ITR and 3' ITR were positioned head-to-tail. The organization of the Ad5 ITRs was based on reports that suggest circular Ad genomes that have the terminal ends fused together head-to-tail are infectious to levels comparable to linear Ad genomes. A minigene encoding the CMV enhancer, an SD/SA sequence, the LacZ gene, and the poly A sequence was inserted immediately following the 5' ITR. The DNA sequence of the resulting plasmid and the sequences for the individual components are reported in Fig. 5 and SEQ ID NO: 2 (see also, brief description of Fig. 5). This plasmid does not require enzymatic digestion prior to its use to produce the viral particle (see Example 3). This vector was designed to enable restriction-independent production of LacZ Ad vectors.

20 Example 2 - Construction of a Helper Virus

The Ad.CBhpAP helper virus [K. Kozarsky et al, Som. Cell Mol. Genet., 19(5):449-458 (1993)] is a replication deficient adenovirus containing an alkaline phosphatase minigene. Its construction involved conventional cloning and homologous recombination techniques. The adenovirus DNA substrate was extracted from CsCl purified d17001 virions, an Ad5 (serotype subgroup C) variant that carries a 3 kb deletion between mu 78.4 through 86 in the nonessential E3 region (provided by Dr. William Wold, Washington University, St. Louis, Missouri). Viral DNA was prepared for co-transfection by digestion with ClaI (adenovirus genomic bp position 917) which removes the left arm of the genome encompassing adenovirus map units 0-2.5. See lower diagram of Fig. 1B.

A parental cloning vector, pAd.BglII was designed. It contains two segments of wild-type Ad5 genome (i.e., map units 0-1 and 9-16.1) separated by a unique BglII cloning site for insertion of heterologous sequences.

- 5 The missing Ad5 sequences between the two domains (adenovirus genome bp 361-3327) results in the deletion of Ela and the majority of Elb following recombination with viral DNA.

- A recombinant hpAP minigene was designed and
10 inserted into the BglII site of pAd.BglII to generate the complementing plasmid, pAdCBhpAP. The linear arrangement of this minigene includes:

- (a) the chicken cytoplasmic β -actin promoter [nucleotides +1 to +275 as described in T. A. Kost et al,
15 Nucl. Acids Res., 11(23):8287 (1983); nucleotides 9241-8684 of Fig. 7];

- (b) an SV40 intron (e.g., nucleotides 1579-1711 of SEQ ID NO: 2),

- (c) the sequence for human placental alkaline
20 phosphatase (available from Genbank) and

- (d) an SV40 polyadenylation signal (a 237 Bam HI-BclI restriction fragment containing the cleavage/poly-A signals from both the early and late transcription units; e.g., nucleotides 837-639 of SEQ ID NO: 1).

- 25 The resulting complementing plasmid, pAdCBhpAP contained a single copy of recombinant hpAP minigene flanked by adenovirus coordinates 0-1 on one side and 9.2-16.1 on the other.

- Plasmid DNA was linearized using a unique NheI site
30 immediately 5' to adenovirus map unit zero (0) and the above-identified adenovirus substrate and the complementing plasmid DNAs were transfected to 293 cells [ATCC CRL1573] using a standard calcium phosphate transfection procedure [see, e.g., Sambrook et al, cited
35 above]. The end result of homologous recombination

involving sequences that map to adenovirus map units 9-16.1 is hybrid Ad.CBhpAP helper virus which contains adenovirus map units 0-1 and, in place of the E1a and E1b coding regions from the d17001 adenovirus substrate, is the hpAP minigene from the plasmid, followed by Ad sequences 9 to 100, with a deletion in the E3 (78.4-86 mu) regions.

Example 3 - Production of Recombinant AdA Virus

The recombinant AdA virus of this invention are generated by co-transfection of a shuttle vector with the helper virus in a selected packaging or non-packaging cell line.

As described in detail below, the linear fragment provided in Example 1A, or the circular AdA genome carrying the LacZ of Example 1B, is packaged into the Ad.CBhpAP helper virus (Example 2) using conventional techniques, which provides an empty capsid head, as illustrated in Fig. 2C. Those virus particles which have successfully taken up the pAd shuttle genome into the capsid head can be distinguished from those containing the hpAP gene by virtue of the differential expression of LacZ and hpAP.

In more detail, 293 cells (4×10^7 pfu 293 cells/150 mm dish) were seeded and infected with helper virus Ad.CBhpAP (produced as described in Example 2) at an MOI of 5 in 20 ml DMEM/2% fetal bovine serum (FBS). This helper specific marker is critical for monitoring the level of helper virus contamination in AdA preparations before and after purification. The helper virus provides in trans the necessary helper functions for synthesis and packaging of the AdΔCMVLacZ genome.

Two hours post infection, using either the restriction-dependent shuttle vector or the restriction-independent shuttle vector, plasmid pAdΔ.CMVLacZ

(digested with EcoRI) or pAdΔc.CMVlacZ DNA, each carrying a LacZ minigene, was added to the cells by a calcium phosphate precipitate (2.5 ml calcium phosphate transfection cocktail containing 50 µg plasmid DNA).

5 Thirty to forty hours post-transfection, cells were harvested, suspended in 10 mM Tris-Cl (pH 8.0) (0.5 ml/150 mm plate) and frozen at -80°C. Frozen cell suspensions were subjected to three rounds of freeze (ethanol-dry ice)-thaw (37°C) cycles to release virion
10 capsids. Cell debris was removed by centrifugation (5,000xg for 10 minutes) and the clarified supernatant applied to a CsCl gradients to separate recombinant virus from helper virus as follows.

 Supernatants (10 ml) applied to the discontinuous
15 CsCl gradient (composed of equal volumes of CsCl at 1.2 g/ml, 1.36 g/ml, and 1.45 g/ml 10 mM Tris-Cl (pH 8.0)) were centrifuged for 8 hours at 72,128Xg, resulting in separation of infectious helper virus from incompletely
20 formed virions. Fractions were collected from the interfacing zone between the helper and top components and analyzed by Southern blot hybridization or for the presence of LacZ transducing particles. For functional
25 analysis, aliquots (2.0 ml from each sample) from the same fractions were added to monolayers of 293 cells (in 35 mm wells) and expression of recombinant β-galactosidase determined 24 hours later. More
30 specifically, monolayers were harvested, suspended in 0.3 ml 10 mM Tris-Cl (pH 8.0) buffer and an extract prepared by three rounds of freeze-thaw cycles. Cell debris was removed by centrifugation and the supernatant tested for
 β-galactosidase (LacZ) activity according to the procedure described in J. Price et al, Proc. Natl. Acad. Sci., USA, 84:156-160 (1987). The specific activity (milliunits β-galactosidase/mg protein or reporter

enzymes was measured from indicator cells. For the recombinant virus, specific activity was 116.

Fractions with β -galactosidase activity from the discontinuous gradient were sedimented through an equilibrium cesium gradient to further enrich the preparation for AdA virus. A linear gradient was generated in the area of the recombinant virus spanning densities 1.29 to 1.34 gm/ml. A sharp peak of the recombinant virus, detected as the appearance of the β -gal activity in infected 293 cells, eluted between 1.31 and 1.33 gm/dl. This peak of recombinant virus was located between two major A_{260} nm absorbing peaks and in an area of the gradient with the helper virus was precipitously dropping off. The equilibrium sedimentation gradient accomplished another 102 to 103 fold purification of recombinant virus from helper virus. The yield of recombinant AdA.CMVLacZ virus recovered from a 50 plate prep after 2 sedimentations ranged from 107 to 108 transducing particles.

Analysis of lysates of cells transfected with the recombinant vector and infected with helper revealed virions capable of transducing the recombinant minigene contained within the vector. Subjecting aliquots of the fractions to Southern analysis using probes specific to the recombinant virus or helper virus revealed packaging of multiple molecular forms of vector derived sequence. The predominant form of the deleted viral genome was the size (~5.5 kb) of the corresponding double stranded DNA monomer (AdA.CMVLacZ) with less abundant but discrete higher molecular weight species (~10 kb and ~15 kb) also present. Full-length helper virus is 35kb. Importantly, the peak of vector transduction activity corresponds with the highest molecular weight form of the deleted virus. These results confirm the hypothesis that ITRs and contiguous packaging sequence are the only elements

necessary for incorporation into virions. An apparently ordered or preferred rearrangement of the recombinant Ad monomer genome leads to a more biologically active molecule. The fact that larger molecular species of the
5 deleted genome are 2x and 3x 10⁶ larger than the monomer deleted virus genome suggests that the rearrangements may involve sequential duplication of the original genome.

These same procedures may be adapted for production of a recombinant AdA virus using a crippled helper virus
10 or helper virus conjugate as described previously.

Example 4 - Recombinant AdA Virus Containing a
Therapeutic Minigene

To test the versatility of the recombinant AdA virus
15 system, the reporter LacZ minigene obtained from pAdΔCMVLacZ was cassette replaced with a therapeutic minigene encoding CFTR.

The minigene contained human CFTR cDNA [Riordan et al, Science, 245:1066-1073 (1989); nucleotides 8622-4065
20 of SEQ ID NO: 3] under the transcriptional control of a chimeric CMV enhancer/chicken β-actin promoter element (nucleotides +1 to +275 as described in T. A. Kost et al, Nucl. Acids Res., 11(23):8287 (1983); nucleotides 9241-8684 of SEQ ID NO: 3, Fig. 7); and followed by an SV-40
25 poly-A sequence (nucleotides 3887-3684 of SEQ ID NO: 3, Fig. 7).

The CFTR minigene was inserted into the E1 deletion site of an Ad5 virus (called pAd.E1Δ) which contains a deletion in E1a from mu 1-9.2 and a deletion in E3 from
30 mu 78.4-86.

The resulting shuttle vector called pAdΔ.CBCFTR (see Figs. 6 and the DNA sequence of Fig. 7 [SEQ ID NO: 3]) used the same Ad ITRs of pAdΔCMVLacZ, but the Ad5 sequences terminated with NheI sites instead of EcoRI.

Therefore release of the minigene from the plasmid was accomplished by digestion with NheI.

The vector production system described in Example 3 was employed, using the helper virus Ad.CBhpAP (Example 2). Monolayers of 293 cells grown to 80-90% confluency in 150 mm culture dishes were infected with the helper virus at an MOI of 5. Infections were done in DMEM supplemented with 2% FBS at 20 ml media/150 mm plate. Two hours post-infection, 50 µg plasmid DNA in 2.5 ml transfection cocktail was added to each plate and evenly distributed.

Delivery of the pAdΔ.CBCFTR plasmid to 293 cells was mediated by formation of a calcium phosphate precipitate and AdΔ.CBCFTR virus resolved from Ad.CBhpAP helper virus by CsCl buoyant density ultracentrifugation as follows:

Cells were left in this condition for 10-14 h, after which the infection/transfection media was replaced with 20 ml fresh DMEM/2% FBS. Approximately 30 h post-transfection, cells were harvested, suspended in 10 mM Tris-Cl (pH 8.0) buffer (0.5 ml/150 mm plate), and stored at -80°C.

Frozen cell suspensions were lysed by three sequential rounds of freeze (ethanol-dry ice)-thaw (37°C). Cell debris was removed by centrifugation (5,000 x g for 10 min) and 10 ml clarified extract layered onto a CsCl step gradient composed of three 9.0 ml tiers with densities 1.45 g/ml, 1.36 g/ml, and 1.20 g/ml CsCl in 10 mM Tris-Cl (pH 8.0) buffer. Centrifugation was performed at 20,000 rpm in a Beckman SW-28 rotor for 8 h at 4°C. Fractions (1.0 ml) were collected from the bottom of the centrifuge tube and analyzed for rAd transducing vectors. Peak fractions were combined and banded to equilibrium. Fractions containing transducing virions were dialyzed against 20 mM HEPES (pH 7.8)/150 mM NaCl

(HBS) and stored frozen at -80°C in the presence of 10% glycerol or as a liquid stock at -20°C (HBS+40% glycerol).

Fractions collected after ultracentrifugation were
5 analyzed for transgene expression and vector DNA. For
lacZ ArAd vectors, 2 μl aliquots were added to 293 cell
monolayers seeded in 35 mm culture wells. Twenty-four
hours later cells were harvested, suspended in 0.3 ml 10
mM Tris-Cl (pH 8.0) buffer, and lysed by three rounds of
10 freeze-thaw. Cell debris was removed by centrifugation
(15,000 x g for 10 min) and assayed for total protein
[Bradford, (1976)] and β -galactosidase activity [Sambrook
et al, (1989)] using ONPG (o-Nitrophenyl β -D-
galactopyranoside) as substrate.

15 Expression of CFTR protein from the AdA.CBCFTR
vector was determined by immunofluorescence localization.
Aliquots of AdA.CBCFTR, enriched by two-rounds of
ultracentrifugation and exchanged to HBS storage buffer,
were added to primary cultures of airway epithelial cells.
20 obtained from the lungs of CF transplant recipients.
Twenty-four hours after the addition of vector, cells
were harvested and affixed to glass slides using
centrifugal force (Cytospin 3, Shandon Scientific
Limited). Cells were fixed with freshly prepared 3%
25 paraformaldehyde in PBS (1.4 mM KH_2PO_4 , 4.3 mM Na_2HPO_4 ,
2.7 mM KCl, and 137 mM NaCl) for 15 min at room
temperature (RT), washed twice in PBS, and permeabilized
with 0.05% NP-40 for 10 min at RT. The
immunofluorescence procedure began with a blocking step
30 in 10% goat serum (PBS/GS) for 1 h at RT, followed by
binding of the primary monoclonal mouse anti-human CFTR
(R-domain specific) antibody (Genzyme) diluted 1:500 in
PBS/GS for 2 h at RT. Cells were washed extensively in
PBS/GS and incubated for 1 h at RT with a donkey anti-
35 mouse IgG (H+L) FITC conjugated

antibody (Jackson ImmunoResearch Laboratories) diluted 1:100 in PBS/GS.

For Southern analysis of vector DNA, 5 μ l aliquots were taken directly from CsCl fractions and incubated with 20 μ l capsid digestion buifer (50 mM Tris-Cl, pH 8.0; 1.0 mM EDTA, pH 8.0; 0.5% SDS, and 1.0 mg/ml Proteinase K) at 50°C for 1 h. The reactions were allowed to cool to RT, loading dye was added, and electrophoresed through a 1.2% agarose gel. Resolved DNAs were electroblotted onto a nylon membrane (Hybond-N) and hybridized with a 32-P labeled restriction fragment. Blots were analyzed by autoradiography or scanned on a Phosphorimager 445 SI (Molecular Dynamics).

The results that were obtained from Southern blot analysis of gradient fractions revealed a distinct viral band that migrated faster than the helper Ad.CBhpAP DNA. The highest viral titers mapped to fractions 3 and 4. Quantitation of the bands in fraction 4 indicated the titer of Ad.CBhpAP was approximately 1.5x greater than AdACBCFTR. However, if the size difference between the two viruses is factored in (Ad.CBhpAP=35 kb; AdACBCFTR=6.2 kb), the viral titer (where 1 particle=1 DNA molecule) of AdACB.CFTR is at least 4-fold greater than the viral titer of Ad.CBhpAP.

While Southern blot analysis of gradient fractions was useful for showing the production of AdA viral particles, it also demonstrated the utility of ultracentrifugation for purifying AdA viruses. Considering the latter of these, both LacZ and CFTR transducing viruses banded in CsCl to an intermediate density between infectious adenovirus helper virions (1.34 g/ml) and incompletely formed capsids (1.31 g/ml). The lighter density relative to helper virus likely results from the smaller genome carried by the AdA viruses. This further suggests changes in virus size

influences the density and purification of AdA virus. Regardless, the ability to separate AdA virus from the helper virus is an important observation and suggests further purification may be achieved by successive rounds of banding through CsCl.

This recombinant virus is useful in gene therapy alone, or preferably, in the form of a conjugate prepared as described herein.

Example 5 - Correction of Genetic Defect in CF airway Epithelial Cells with AdACB.CFTR

Treatment of cystic fibrosis, utilizing the recombinant virus provided above, is particularly suited for *in vivo*, lung-directed, gene therapy. Airway epithelial cells are the most desirable targets for gene transfer because the pulmonary complications of CF are usually its most morbid and life-limiting.

The recombinant AdACB.CFTR virus was fractionated on sequential CsCl gradients and fractions containing CFTR sequences, migrating between the adenovirus and top components fractions described above were used to infect primary cultures of human airway epithelial cells derived from the lungs of a CF patient. The cultures were subsequently analyzed for expression of CFTR protein by immunocytochemistry. Immunofluorescent detection with mouse anti-human CFTR (R domain specific) antibody was performed 24 hours after the addition of the recombinant virus. Analysis of mock infected CF cells failed to reveal significant binding to the R domain specific CFTR antibody. Primary airway epithelium cultures exposed to the recombinant virus demonstrated high levels of CFTR protein in 10-20% of the cells.

Thus, the recombinant virus of the invention, containing the CFTR gene, may be delivered directly into the airway, e.g. by a formulating the virus above, into a

preparation which can be inhaled. For example, the recombinant virus or conjugate of the invention containing the CFTR gene, is suspended in 0.25 molar sodium chloride. The virus or conjugate is taken up by respiratory airway cells and the gene is expressed.

Alternatively, the virus or conjugates of the invention may be delivered by other suitable means, including site-directed injection of the virus bearing the CFTR gene. In the case of CFTR gene delivery, preferred solutions for bronchial instillation are sterile saline solutions containing in the range of from about 1×10^7 to 1×10^{10} pfu/ml, more particularly, in the range of from about 1×10^8 to 1×10^9 pfu/ml of the virus of the present invention.

Other suitable methods for the treatment of cystic fibrosis by use of gene therapy recombinant viruses of this invention may be obtained from the art discussions of other types of gene therapy vectors for CF. See, for example, U. S. Patent No. 5,240,846, incorporated by reference herein.

Example 6 - Synthesis of Polycation Helper Virus Conjugate

Another version of the helper virus of this invention is a polylysine conjugate which enables the pAdA shuttle plasmid to complex directly with the helper virus capsid. This conjugate permits efficient delivery of shuttle plasmid pAdA shuttle vector in tandem with the helper virus, thereby removing the need for a separate transfection step. See, Fig. 10 for a diagrammatic outline of this construction. Alternatively, such a conjugate with a plasmid supplying some Ad genes and the helper supplying the remaining necessary genes for production of the AdA viral vector provides a novel way

to reduce contamination of the helper virus, as discussed above.

Purified stocks of a large-scale expansion of Ad.CBhpAP were modified by coupling poly-L-lysine to the virion capsid essentially as described by K. J. Fisher and J. M. Wilson, Biochem. J., 299:49-58 (1994), resulting in an Ad.CBhpAP-(Lys)_n conjugate. The procedure involves three steps.

First, CsCl band purified helper virus Ad.CBhpAP was reacted with the heterobifunctional crosslinker sulfo-SMCC [sulfo-(N-succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate] (Pierce). The conjugation reaction, which contained 0.5 mg (375 nmol) of sulfo-SMCC and 6×10^{12} A₂₆₀ helper virus particles in 3.0 ml of HBS, was incubated at 30°C for 45 minutes with constant gentle shaking. This step involved formation of a peptide bond between the active N-hydroxysuccinimide (NHS) ester of sulfo-SMCC and a free amine (e.g. lysine) contributed by an adenovirus protein sequence (capsid protein) in the vector, yielding a maleimide-activated viral particle. The activated adenovirus is shown in Fig. 10 having the capsid protein fiber labeled with the nucleophilic maleimide moiety. In practice, other capsid polypeptides including hexon and penton base are also targeted.

Unincorporated, unreacted cross-linker was removed by gel filtration on a 1 cm x 15 cm Bio-Gel P-6DG (Bio-Rad Laboratories) column equilibrated with 50 mM Tris/HCl buffer, pH 7.0, and 150 mM NaCl. Peak A₂₆₀ fractions containing maleimide-activated helper virus were combined and placed on ice.

Second, poly-L-lysine having a molecular mass of 58 kDa at 10 mg/ml in 50 mM triethanolamine buffer (pH 8.0), 150 mM NaCl and 1 mM EDTA was thiolated with 2-iminothiolane/HCl (Traut's Reagent; Pierce) to a molar

ratio of 2 moles-SH/mole polylysine under N_2 ; the cyclic thioimide reacts with the poly(L-lysine) primary amines resulting in a thiolated polycation. After a 45 minute incubation at room temperature the reaction was applied to a 1 cm x 15 cm Bio-Gel P6DG column equilibrated with 50 mM Tris/HCl buffer (pH 7.0), 150 mM NaCl and 2 mM EDTA to remove unincorporated Traut's Reagent.

Quantification of free thiol groups was accomplished with Ellman's reagent [5,5'-dithio-bis-(2-nitrobenzoic acid)], revealing approximately 3-4 mol of -SH/mol of poly(L-lysine). The coupling reaction was initiated by adding 1×10^{12} A_{260} particles of maleimide-activated helper virus/mg of thiolated poly(L-lysine) and incubating the mixture on ice at 4°C for 15 hours under argon. 2-mercaptoethylamine was added at the completion of the reaction and incubation carried out at room temperature for 20 minutes to block unreacted maleimide sites.

Virus-polylysine conjugates, Ad.CPAP-p(Lys)_n, were purified away from unconjugated poly(L-lysine) by ultracentrifugation through a CsCl step gradient with an initial composition of equal volumes of 1.45 g/ml (bottom step) and 1.2 g/ml (top step) CsCl in 10 mM Tris/HCl buffer (pH 8.0). Centrifugation was at 90,000 g for 2 hours at 5°C. The final product was dialyzed against 20 mM Hepes buffer (pH 7.8) containing 150 mM NaCl (HBS).

Example 7 - Formation of AdΔ/helper-pLys Viral Particle

The formation of Ad.CBhpAP-pLys/pAdΔ.CMVlacZ particle is initiated by adding 20 µg plasmid pAdΔ.CMVlacZ DNAs to 1.2×10^{12} A_{260} particles Ad.CBhpAP-pLys in a final volume of 0.2 ml DMEM and allowing the complex to develop at room temperature for between 10-15 minutes. This ratio typically represents the plasmid DNA binding capacity of a standard lot of adenovirus-pLys

conjugate and gives the highest levels of plasmid transgene expression.

The resulting trans-infection particle is transfected onto 293 cells (4×10^7 cells seeded on a 150 mm dish). Thirty hours after transfection, the particles are recovered and subjected to a freeze/thaw technique to obtain an extract. The extract is purified on a CsCl step gradient with gradients at 1.20 g/ml, 1.36 g/ml and 1.45 g/ml. After centrifugation at $90,000 \times g$ for 8 hours, the AdA vectors were obtained from a fraction under the top components as identified by the presence of LacZ, and the helper virus was obtained from a smaller, denser fraction, as identified by the presence of hpAP.

Example 8 - Construction of Modified Helper Viruses with Crippled Packaging (PAC) Sequences

This example refers to Figs. 9A through 9C, 10A and 10B in the design of modified helper viruses of this invention.

Ad5 5' terminal sequences that contained PAC domains I and II (Fig. 8A) or PAC domains I, II, III, and IV (Fig. 8B) were generated by PCR from the wild type Ad5 5' genome depicted in Fig. 1B using PCR clones indicated by the arrows in Fig. 1B. The resulting amplification products (Fig. 8A and 8B) sequences differed from the wild-type Ad5 genome in the number of A-repeats carried by the left (5') end.

As depicted in Fig. 8C, these amplification products were subcloned into the multiple cloning site of pAd.Link.1 (IHGT Vector Core). pAd.Link.1 is a adenovirus based plasmid containing adenovirus m.u. 9.6 through 16.1. The insertion of the modified PAC regions into pAd.Link.1 generated two vectors pAd.PACII (containing PAC domains I and II) and pAd.PACIV (containing PAC domains I, II, III, and IV).

Thereafter, as depicted in Figs. 10A and 10B, for each of these plasmids, a human placenta alkaline phosphatase reporter minigene containing the immediate early CMV enhancer/promoter (CMV), human placenta alkaline phosphatase cDNA (hpa^L), and SV40 polyadenylation signal (pA), was subcloned into each PAC vector, generating pAd.PACII.CMVhpaP and pAd.PACIV.CMVhpaP, respectively.

These plasmids were then used as substrates for homologous recombination with dl7001 virus, described above, by co-transfection into 293 cells. Homologous recombination occurred between the adenovirus map units 9-16 of the plasmid and the crippled Ad5 virus. The results of homologous recombination were helper viruses containing Ad5 5' terminal sequences that contained PAC domains I and II or PAC domains I, II, III, and IV, followed by the minigene, and Ad5 3' sequences 9.6-78.3 and 87-100. Thus, these crippled viruses are deleted of the E1 gene and the E3 gene.

The plaque formation characteristics of the PAC helper viruses gave an immediate indication that the PAC modifications diminished the rate and extent of growth. Specifically, PAC helper virus plaques did not develop until day 14-21 post-transfection, and on maturation remained small. From previous experience, a standard first generation Ad.CBhpaP helper virus with a complete left terminal sequence would begin to develop by day 7 and mature by day 10.

Viral plaques were picked and suspended in 0.5 ml of DMEM media. A small aliquot of the virus stock was used to infect a fresh monolayer of 293 cells and histochemically stained for recombinant alkaline phosphatase activity 24 hours post-infection. Six of eight Ad.PACIV.CMVhpaP (encodes A-repeats I-IV) clones that were screened for transgene expression were

positive, while all three Ad.PACII.CMVhpAP clones that were selected scored positive. The clones have been taken through two rounds of plaque purification and are currently being expanded to generate a working stock.

- 5 These crippled helper viruses are useful in the production of the AdA virus particles according to the procedures described in Example 3. They are characterized by containing sufficient adenovirus genes to permit the packaging of the shuttle vector genome, but
10 their crippled PAC sequences reduce their efficiency for self-encapsidation. Thus less helper viruses are produced in favor of more AdA recombinant viruses. Purification of AdA virus particles from helper viruses is facilitated in the CsCl gradient, which is based on
15 the weight of the respective viral particles. This facility in purification is a decided advantage of the AdA vectors of this invention in contrast to adenovirus vectors having only E1 or smaller deletions. The AdA vectors even with minigenes of up to about 15 kb are
20 significantly different in weight than wild type or other adenovirus helpers containing many adenovirus genes.

Example 9 - AdA Vector Containing a full-length dystrophin transgene

- 25 Duchenne muscular dystrophy (DMD) is a common x-linked genetic disease caused by the absence of dystrophin, a 427K protein encoded by a 14 kilobase transcript. Lack of this important sarcolemmal protein leads to progressive muscle wasting, weakness, and death.
30 One current approach for treating this lethal disease is to transfer a functional copy of the dystrophin gene into the affected muscles. For skeletal muscle, a replication-defective adenovirus represents an efficient delivery system.

According to the present invention, a recombinant plasmid pAdΔ.CMVmdys was created which contains only the Ad5 cis-elements (i.e., ITRs and contiguous packaging sequences) and harbors the full-length murine dystrophin gene driven by the CMV promoter. This plasmid was generated as follows.

PSL1180 [Pharmacia Biotech] was cut with Not I, filled in by Klenow, and religated thus ablating the Not I site in the plasmid. The resulting plasmid is termed pSL1180NN and carries a bacterial ori and Amp resistance gene.

pAdΔ.CMVLacZ of Example 1 was cut with EcoRI, klenowed, and ligated with the ApaI-cut pSL1180NN to form pAdΔ.CMVLacZ (ApaI).

The 14 kb mouse dystrophin cDNA [sequences provided in C. C. Lee et al, Nature, 349:334-336 (1991)] was cloned in two large fragments using a lambda ZAP cloning vector (Stratagene) and subsequently cloned into the bluescript vector pSK- giving rise to the plasmid pCCL-DMD. A schematic diagram of this vector is provided in Fig. 11, which illustrates the restriction enzyme sites.

pAdΔ.CMVLacZ (ApaI) was cut with NotI and the large fragment gel isolated away from the lacZ cDNA. pCCL-DMD was also cut with NotI, gel isolated and subsequently ligated to the large NotI fragment of NotI digested pAdΔ.CMVLacZ (ApaI). The sequences of resulting vector, pAdΔ.CMVmdys, are provided in Fig. 12A-12P [SEQ ID NO:10].

This plasmid contains sequences from the left-end of the Ad5 encompassing bp 1-360 (5' ITR), a mouse dystrophin minigene under the control of the CMV promoter, and sequence from the right end of Ad5 spanning

bp 35353 to the end of the genome (3' ITR). The minigene is followed by an SV-40 poly-A sequence similar to that described for the plasmids described above.

The vector production system described herein is employed. Ten 150mm 293 plates are infected at about 90% confluency with a reporter recombinant E1-deleted virus Ad.CBhpAP at an MOI of 5 for 60 minutes at 37°C. These cells are transfected with pAdΔ.CMVmDys by calcium phosphate co-precipitation using 50 µg linearized DNA/dish for about 12-16 hours at 37°C. Media is replaced with DMEM + 10% fetal bovine serum.

Full cytopathic effect is observed and a cell lysate is made by subjecting the cell pellet to freeze-thaw procedures three times. The cells are subjected to an SW41 three tier CsCl gradient for 2 hours and a band migrating between the helper adenovirus and incomplete virus is detected.

Fractions are assayed on a 6 well plate containing 293 cells infected with 5λ of fraction for 16-20 hours in DMEM + 2% FBS. Cells are collected, washed with phosphate buffered saline, and resuspended in 2 ml PBS. 200λ of the 2ml cell fractions is cytopun onto a slide.

The cells were subjected to immunofluorescence for dystrophin as follows. Cells were fixed in 10N MeOH at -20°C. The cells were exposed to a monoclonal antibody specific for the carboxy terminus of human dystrophin [NCL-DYS2; Novocastra Laboratories Ltd., UK]. Cells were then washed three times and exposed to a secondary antibody, i.e. 1:200 goat anti-mouse IgG in FITC.

The titer/fraction for seven fractions revealed in the immunofluorescent stains were calculated by the following formula and reported in Table 2 below.

$$\text{DFU/field} = (\text{DFU}/200\lambda \text{ cells}) \times 10 = \text{DFU}/10^6 \text{ cells} =$$
$$(\text{DFU}/5\lambda \text{ viral fraction}) \times 20 = \text{DFU}/100\lambda \text{ fraction.}$$

Table 2

	<u>Fraction</u>	<u>DFU/100λ</u>
	1	--
5	2	--
	3	6×10^3
	4	1.8×10^4
10	5	9.6×10^3
	6	200
15	7	200

A virus capable of transducing the dystrophin minigene is detected as a "positive" (i.e., green fluorescent) cell. The results of the IF illustrate that heat-treated fractions do not show positive immunofluorescence. Southern blot data suggest one species on the same size as the input DNA, with helper virus contamination.

The recombinant virus can be subsequently separated from the majority of helper virus by sedimentation through cesium gradients. Initial studies demonstrate that the functional AdCMV Δ mDys virions are produced, but are contaminated with helper virus. Successful purification would render Ad Δ virions that are incapable of encoding viral proteins but are capable of transducing murine skeletal muscle.

Example 10 - Pseudotyping

The following experiment provides a method for preparing a recombinant Ad Δ according to the invention, utilizing helper viruses from serotypes which differ from that of the pAd Δ in the transfection/infection protocol. It is unexpected that the ITRs and packaging sequence of

Ad5 could be incorporated into a virion of another serotype.

A. Protocol

The basic approach is to transfect the
5 AdΔ.CMVlacZ recombinant virus (Ad5) into 293 cells and subsequently infect the cell with the helper virus derived from a variety of Ad serotypes (2, 3, 4, 5, 7, 8, 12, and 40). When CPE is achieved, the lysate is harvested and banded through two cesium gradients.
10 More particularly, the Ad5-based plasmid pAdΔ.CMVlacZ of Example 1 was linearized with EcoRI. The linearized plasmids were then transfected into ten 150 mm dishes of 293 cells using calcium phosphate co-precipitation. At 10-15 hours post transfection, wild
15 type adenoviruses (of one of the following serotypes: 2, 3, 4, 5, 7, 12, 40) were used to infect cells at an MOI of 5. The cells were then harvested at full CPE and lysed by three rounds of freeze-thawing. Pellet is resuspended in 4 mL Tris-HCl. Cell debris was removed by
20 centrifugation and partial purification of Ad5Δ.CMVlacZ from helper virus was achieved with 2 rounds of CsCl gradient centrifugation (SW41 column, 35,000 rpm, 2 hours). Fractions were collected from the bottom of the tube (fraction #1) and analysed for lacZ transducing
25 viruses on 293 target cells by histochemical staining (at 20h PI). Contaminating helper viruses were quantitated by plaque assay.

Except for adenovirus type 3, infection with Ad serotypes 2, 4, 5, 7, 12 and 40 were able to produce lacZ
30 transducing viruses. The peak of β-galactosidase activity was detected between the two major A₂₆₀ absorbing peaks, where most of the helper viruses banded (data not shown). The quantity of lacZ virus recovered from 10 plates ranged from 10⁴ to 10⁸ transducing
35 particles depending on the serotype of the helper. As

expected Ad2 and Ad5 produced the highest titer of *lacZ* transducing viruses (Table 3). Wild type contamination was in general 10^2 - 10^3 log higher than corresponding *lacZ* titer except in the case of Ad40.

B. Results

Table 3 summarizes the growth characteristics of the wild type adenoviruses as evaluated on propagation in 293 cells. This demonstrated the feasibility of utilizing these helper viruses to infect the cell line which has been transfected with the Ad5 deleted virus.

Table 3

Adenovirus serotypes		p/ml	pfu/ml	p:pfu
15	2	5×10^{12}	2.5×10^{11}	20:01
	3	1×10^{12}	6.25×10^9	160:1
	4	3×10^{12}	2×10^9	150:1
20	5	1×10^{12}	5×10^{10}	20:01
	7a	5×10^{12}	1×10^{11}	50:1
25	12	6×10^{11}	4×10^9	150:1
	35	1.2×10^{12}		
30	40	2.2×10^{12}	4.4×10^8	5000:1

Table 4 summarizes the results of the final purified fractions. The middle column, labeled LFU/ μ l quantifies the production of *lacZ* forming units, which is a direct measure of the packaging and propagation of pseudotyped recombinant AdA virus. The pfu/ μ l titer is an estimate of the contaminating wild type virus. AdA virus pseudotyped with all adenoviral strains was generated except for Ad3. The titers range between 10^7 - 10^4 .

53

Table 4

	Serotypes	LFU/ml	PFU/ml
5	2	4.6×10^7	1.8×10^9
	3	0	NA
10	4	6.7×10^6	9.3×10^7
	5	6.3×10^7	1.9×10^9
	7a	3×10^6	1.8×10^8
15	12	1.2×10^5	3.3×10^8
	40	9.5×10^4	1.5×10^3
20			

Table 5A-5D represents a more detailed analysis of the fractions from the second purification for each of the experiments summarized in Table 4. Again, LFU/ μ l is the recovery of the AdA viruses, whereas pfu/ μ l represents recovery of the helper virus.

Table 5A

	Ad2 Fraction #	VOLUME/ μ l	LFU/ μ l	PFU/ μ l
30	1	120	9532	8×10^6
	2	100	5.8×10^4	3×10^6
35	3	100	8.24×10^4	6×10^5
	4	100	9.47×10^4	1.2×10^5
40	5	100	6×10^4	8×10^4
	6	100	2×10^4	6×10^4
	7	100	5434	5×10^4
45	Total/10 pH		3.32×10^7	1.35×10^9

50

Table 5B

5	Ad4 Fraction #	VOLUME/ul	LFU/ul	PFU/ul
	1	100	1000	1.75×10^5
10	2	100	1.79×10^4	2.8×10^5
	3	100	1.8×10^4	5.5×10^4
15	4	100	2909	1.25×10^4
	5	100	920	4×10^4
	6	100	153	3×10^3
20	Total/10 pH		4×10^6	5.6×10^7
25	Ad5 Fraction #			
	1	120	1.98×10^4	6×10^6
	2	100	5.8×10^4	3×10^6
30	3	100	1.2×10^5	1.5×10^6
	4	100	1×10^5	1.4×10^5
35	5	100	7.96×10^4	8×10^4
	6	100	6860	6×10^4
40	Total/10 pH		3.88×10^7	1.2×10^9

55

Table 5C

5	Ad7 Fraction #	VOLUME/ul	LFU/ul	PFU/ul
10	1	100	1225	5×10^5
	2	100	5550	4×10^5
	3	100	4938	2×10^5
	4	100	3866	8×10^4
15	5	100	4134	6×10^4
	6	100	995	7×10^4
20	7	100	230	6×10^3
	Total/10 pH		2.09×10^6	1.3×10^8
25	Ad12 Fraction #			
30	1	100	31	5×10^5
	2	80	169	8.5×10^5
	3	80	245	1.8×10^5
	4	110	161	1.1×10^5
35	5	120	62	7×10^3
	Total/10 pH		6.14×10^4	1.65×10^8

56

Table 5D

	Ad40 Fraction #	VOLUME/ul	LFU/ul	PFU/ul
5	1	80	61	5
	2	80	184	3
10	3	80	199	3
	4	80	168	1
	5	80	122	
15	6	100	46	
	7	100	32	
20	Total/10 pH		6.65×10^4	1.1×10^3

C. Characterization of the Structure of Packaged

25 Viruses

Aliquots of serial fractions were analysed by Southern blots using lacZ as a probe. In the case of Ad2 and 5, not only the linearized monomer was packaged but multiple forms of recombinant virus with distinct sizes were found. These forms correlated well with the sizes of dimers, trimers and other higher molecular weight concatamers. The linearized monomers peaked closer to the top of tube (the defective adenovirus band) than other forms. When these forms were correlated with lacZ activity, a better correlation was found between the higher molecular weight forms than the monomers. With pseudotyping of Ad4 and Ad7, no linearized monomers were packaged and only higher molecular weight forms were found.

40 These data definitively demonstrate the production and characterization of the Δ virus and the different pseudotypes. This example illustrates a very simple way of generating pseudotype viruses.

Example 11 - AdA Vector Containing a FH Gene

Familial hypercholesterolemia (FH) is an autosomal dominant disorder caused by abnormalities (deficiencies) in the function or expression of LDL receptors [M.S. Brown and J.L. Goldstein, Science, 232(4746):34-37 (1986); J.L. Goldstein and M.S. Brown, "Familial hypercholesterolemia" in Metabolic Basis of Inherited Disease, ed. C.R. Scriver et al, McGraw Hill, New York, pp1215-1250 (1989).] Patients who inherit one abnormal allele have moderate elevations in plasma LDL and suffer premature life-threatening coronary artery disease (CAD). Homozygous patients have severe hypercholesterolemia and life-threatening CAD in childhood. An FH-containing vector of the invention is constructed by replacing the lacZ minigene in the pAdAc.CMVlacZ vector with a minigene containing the LDL receptor gene [T. Yamamoto et al, Cell, 39:27-38 (1984)] using known techniques and as described analogously for the dystrophin gene and CFTR in the preceding examples. Vectors bearing the LDL receptor gene can be readily constructed according to this invention. The resulting plasmid is termed pAdAc.CMV-LDL.

This plasmid is useful in gene therapy of FH alone, or preferably, in the form of a conjugate prepared as described herein to substitute a normal LDL gene for the abnormal allele responsible for the gene.

A. Ex Vivo Gene Therapy

Ex vivo gene therapy can be performed by harvesting and establishing a primary culture of hepatocytes from a patient. Known techniques may be used to isolate and transduce the hepatocytes with the above vector(s) bearing the LDL receptor gene(s). For example, techniques of collagenase perfusion developed for rabbit liver can be adapted for human tissue and used in transduction. Following transduction, the hepatocytes

are removed from the tissue culture plates and reinfused into the patient using known techniques, e.g. via a catheter placed into the inferior mesenteric vein.

B. In Vivo Gene Therapy

5 Desirably, the *in vivo* approach to gene therapy, e.g. liver-directed, involves the use of the vectors and vector conjugates described above. A preferred treatment involves infusing a vector LDL conjugate of this invention into the peripheral
10 circulation of the patient. The patient is then evaluated for change in serum lipids and liver tissues.

The virus or conjugate can be used to infect hepatocytes *in vivo* by direct injection into a peripheral or portal vein (10^7 - 10^8 pfu/kg) or retrograde into the
15 biliary tract (same dose). This effects gene transfer into the majority of hepatocytes.

Treatments are repeated as necessary, e.g. weekly. Administration of a dose of virus equivalent to an MOI of approximately 20 (i.e. 20 pfu/hepatocyte) is
20 anticipated to lead to high level gene expression in the majority of hepatocytes.

All references recited above are incorporated herein by reference. Numerous modifications and variations of the present invention are included in the above-
25 identified specification and are expected to be obvious to one of skill in the art. Such modifications and alternations to the compositions and processes of the present invention, such as various modifications to the PAC sequences or the shuttle vectors, or to other
30 sequences of the vector, helper virus and minigene components, are believed to be encompassed in the scope of the claims appended hereto.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: Trustees of the University of Pennsylvania
Wilson, James M.
Fisher, Krishna J.
Chen, Shu-Jen
Weitzman, Matthew
- (ii) TITLE OF INVENTION: Improved Adenovirus and Methods
of Use Thereof
- (iii) NUMBER OF SEQUENCES: 10
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Howson and Howson
 - (B) STREET: Spring House Corporate Cntr, PO Box 457
 - (C) CITY: Spring House
 - (D) STATE: Pennsylvania
 - (E) COUNTRY: USA
 - (F) ZIP: 19477
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER:
 - (B) FILING DATE:
 - (C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: US 08/331,381
 - (B) FILING DATE: 28-OCT-1994
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Bak, Mary E.
 - (B) REGISTRATION NUMBER: 31,215
 - (C) REFERENCE/DOCKET NUMBER: GNVPN.008PCT
- (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: 215-540-9200
 - (B) TELEFAX: 215-540-5818

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 7897 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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CTTTTTTACA CTGTGACTGA TTGAGCTGGT GCCGTGTCGA GTGGTGTFFF	400
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CAGTTAATAG	TTTGCGCAAC	GTTGTTGCCA	TTGCTACAGG	CATCGTGGTG	6900
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66

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(2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 7852 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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CCTGGGTCGA ACGCTGGAAG GCGGCGGGCC ATTACCAGGC CGAAGCAGCG	4350
TTGTTGCAGT GCACGGCAGA TACACTTGCT GATGCGGTGC TGATTACGAC	4400
CGCTCACGCG TGGCAGCATC AGGGGAAAAC CTTATTTATC AGCCGGAAAA	4450

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GCGGATACAT ATTTGAATGT ATTTAGAAAA ATAAACAAAT AGGGGTTCCG	7750
CGCACATTC CCCGAAAAGT GCCACCTGAC GTCTAAGAAA CCATTATTAT	7800
CATGACATTA ACCTATAAAA ATAGGCGTAT CACGAGGCCC TTTCGTCTTC	7850
AA	7852

(2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 9972 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

TCTTCCGCTT CCTCGCTCAC TGACTCGCTG CGCTCGGTCTG TTCGGCTGCG	50
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CAGGGGATAA CGCAGGAAAG AACATGTGAG CAAAAGGCCA GCAAAGGCC	150
AGGAACCGTA AAAAGGCCGC GTTGCTGGCG TTTTCCATA GGCTCCGCCC	200
CCCTGACGAG CATCACAAAA ATCGACGCTC AAGTCAGAGG TGGCGAAACC	250
CGACAGGACT ATAAAGATAC CAGGCGTTTC CJCCTGGAAG CTCCCTCGTG	300
CGCTCTCCTG TTCCGACCCT GCCGCTTACC GGATACCTGT CCGCCTTTCT	350
CCCTTCGGGA AGCGTGCGC TTTCTCATAG CTCACGCTGT AGGTATCTCA	400
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CAGATTTTAC TTCCTCTTAT TCAGTTTTCC CGCGAAAATG GCCAAATCTT	9350
ACTCGGTTAC GCCCAAATTT ACTACAACAT CCJCCTAAAA CCGCGCGAAA	9400
ATTGTCACTT CCTGTGTACA CCGGCGCACA CCAAAAACGT CACTTTTGCC	9450
ACATCCGTCG CTTACATGTG TTCCGCCACA CTTGCAACAT CACACTTCCG	9500
CCACACTACT ACGTCACCCG CCCC GTTCCC ACGCCCCGCG CCACGTCACA	9550
AACTCCACCC CCTCATTATC ATATTGGCTT CAATCCAAAA TAAGGTATAT	9600
TATTGATGAT GCTAGCATGC GCAAATTTAA AGCGCTGATA TCGATCGCGC	9650
GCAGATCTGT CATGATGATC ATTGCAATTG GATCCATATA TAGGGCCCCG	9700
GTTATAATTA CCTCAGGTCG ACGTCCCATG GCCATTGCGA TTCGTAATCA	9750
TGGTCATAGC TGTTTCCTGT GTGAAATTGT TATCCGCTCA CAATTCCACA	9800
CAACATACGA GCCGGAAGCA TAAAGTGTA AGCCTGGGGT GCCTAATGAG	9850
TGAGCTAACT CACATTAATT GCGTTGCGCT CACTGCCCCG TTTCCAGTCG	9900
GGAAACCTGT CGTGCCAGCT GCATTAATGA ATCGGCCAAC GCGCGGGGAG	9950
AGGCGGTTTG CGTATTGGGC GC	9972

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

TAGTAAATTT GGGC

81

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

AGTAAGATTT GGCC

14

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

AGTGAAATCT GAAT

14

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GAATAATTTT GTGT

14

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: unknown

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82

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

14

CGTAATATTT GTCT

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

8

WANWTTTG

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19307 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CCAATTCCAT CATCAATAAT ATACCTTATT TTGGATTGAA GCCAATATGA	50
TAATGAGGGG GTGGAGTTTG TGACGTGGCG CGGGGCGTGG GAACGGGGCG	100
GGTGACGTAG GTTTTAGGGC GGAGTAACTT GTATGTGTTG GGAATTGTAG	150
TTTTCTTAAA ATGGGAAGTT ACGTAACGTG GGAAAACGGA AGTGACGATT	200
TGAGGAAGTT GTGGGTTTTT TGGCTTTCGT TTCTGGGCGT AGGTTTCGCGT	250
GCGGTTTTCT GGGTGTTTTT TGTGGACTTT AACCGTTACG TCATTTTTTA	300
GTCCTATATA TACTCGCTCT GCACTTGGCC CTTTTTTACA CTGTGACTGA	350
TTGAGCTGGT GCCGTGTCGA GTGGTGTTTT TTTAATAGGT TTTCTTTTTT	400

ACTGGTAAGG	CTGACTGTTA	GGCTGCCGCT	GTGAAGCGCT	GTATGTTGTT	450
CTGGAGCGGG	AGGGTGCTAT	TTTGCCTAGG	CAGGAGGGTT	TTTCAGGTGT	500
TTATGTGTTT	TTCTCTCCTA	TTAATTTTGT	TATACCTCCT	ATGGGGGCTG	550
TAATGTTGTC	TCTACGCCTG	CGGGTATGTA	T.CCCCCCAA	GCTTGCATGC	600
CTGCAGGTCG	ACTCTAGAGG	ATCCGAAAAA	ACCTCCCACA	CCTCCCCCTG	650
AACCTGAAAC	ATAAAATGAA	TGCAATTGTT	GTTGTTAACT	TGTTTATTGC	700
AGCTTATAAT	GGTTACAAAT	AAAGCAATAG	CATCACAAAT	TTCACAAATA	750
AAGCATTTTT	TTCACTGCAT	TCTAGTTGTG	GTTTGTCCAA	ACTCATCAAT	800
GTATCTTATC	ATGTCTGGAT	CCCCGCGGCC	GCTCTAGAAC	TAGTGGATCC	850
CCCCGGCTGC	AGGAATTCCG	TAACATAACT	GCGTGCTTTA	TTGAGATACA	900
CAGTAAAGCA	GTAATATAAT	ACAATAGTAA	GGCATATATT	TGGTGAAATC	950
TGATATGTTG	TGAAAATGCA	GTAAAACTGA	AGTTTAAAAA	AATAATTAGT	1000
AAATGTTACA	GTGTTGGTGT	TAAACACAA	TCTATTATGA	TACTCAAGTA	1050
AGAGTCCAGT	ACCTGGAGAC	AATGATGATA	CATGCCATGT	GATGATTATG	1100
CTTCAGTTAC	ACTGATTATG	ATTTACACTT	TAATACTTGA	TGGTTATAAA	1150
GAACATGAAA	TGATGTCCAA	ATTATGCTTA	AAATCAGCAA	TAAAGCTCTC	1200
AGTTTTTTATT	CAAATATTTT	GATAGATTCA	CTCCAGAACT	AATATCTAAA	1250
AGATAAAACG	AAAAGATTAA	AACAAAATA	TGCACTCTAT	CTACCTTGGA	1300
TTTTAGAATG	AAACTTAAAA	CTTCTTAGTA	GGAAAGGAAC	CCCTTGTTTT	1350
AAATCTTGGT	GAAAACAAAT	CCTTGGATAA	AGAAAATGCC	CAGTGCCACA	1400
TAAAGGAGAG	AGAGAGAGAA	AAGCAAGACC	AGAACCAAAT	TTCAATTTGT	1450
TATCTTAGAG	CTTTGGGTTT	TCTTTTGGAA	ATTATAAATG	AAAAAAGGAA	1500
ACTGGTGTCC	ACACAACAGA	CAAGTGGTGA	AGTTGTGAAA	TTAGGTGTGC	1550
ACAATTACTA	GAAACACCCC	AAAACCAAAG	TGAGGTAGAA	ATAGCATGAG	1600
AAGCTGTGTT	TGATGTTAAT	TACAATTAAT	AATGGACAAA	ACCCACTCGC	1650
TAGAAGTTAA	TTACACTTGA	CGTTAGAGGT	AACAGATTTG	CAAAATGATA	1700

GGACAGTGAT TTCTATTGAG AGAATGCTCT TTAAATGCTA AGAAGAAGAA	1750
ACTGGCATGA GAGGAGTAAA GCTCTTCCTA GCAGTCCTTA GCTTTCTGTT	1800
GCACCTTTTTC TCCTGGTTCA ATGACTTGCA TTTGTTTAGA CATTTTCAGCC	1850
CGTCAACTAG ACCAGAGAGT TTGGAGACGC TTTTGCTCTC AAAACTTTCC	1900
AACCACTGTG CCTTCTCACC CACAATCCTG TGTGGAGTTA CTTGCAGGGA	1950
AACCAATGCA AAGGAGACAA ATGCAGTTCA TGGGCTTCTG GACTGATATT	2000
CACCAGGGTC ACAATGTGAT TGGGTTACTT TCTTAACAGT AATCCTAAGT	2050
CTTGCAGCAT TAAAAAAAAA AATCATCACA ATGAAGAAAA AAAAACCCTA	2100
AAAATCTAAA ATCTAAAATT CATCATCATC ATCAACAACA ACAACAACAA	2150
CAACAACAAA ACCACCCACT TCAGGTTGAG TTTATGAAGA GGGCAGAACA	2200
ATTTAGTTGT AATTATAGAG ATGTTTATAT GTATAGTTGT AAATATTCAT	2250
CCATTCTTTT ACAGAGTTGT TGCTCCCCTC ATATAAATTG ACTGAGGAGC	2300
CGCAACCTTT AGCTCCTACC ATCTTCCTCC TACTGTCTGG GAGTTAAAAA	2350
TGTCATCTGA TGTTCCTATTG CAGAAACATC ATTAAATATA ACCCAACAGT	2400
AGGAAGTTGA ATATATCAGC CAACAAATTA CTATGATAGT AAGTCCTGTG	2450
TATTCATTG CATGTTCTTT GAAAAAATG AATCCTCTAG CTCTCAGTGG	2500
AAAGTTTAAA ACTAGAAACA TCTGGAGCCC TAGACAATAT TTTAGTGTGG	2550
CGGTAGTCTC CTGGCTTTGG GCTCCAGGGA AAATTCATC TTGCCCCAAGC	2600
AGATAAGCCC AGATGACTAG AAGCAATTTC CATTAGGAAG TGGCAAGAAC	2650
ATTTGAAGAA GTAACCTCAT ATCTATTTAT CTATATACCT ATAGTATTTA	2700
TATACTTGTA GACATATAGA TGTATAAAAT GAAAGCCCAT AGCCAGCCCC	2750
ACTCAGTCAA CAATTCTCAA AAGAGCAATA TGAAGCAGTC ATTTGGTGGG	2800
GTTTCGTATGC AAGAAAATAA AAAACGTCA TGAATTCCAT ATGAATACCA	2850
CGCTAAAGTA ATGCAAAACA ATGTGCTGCC TCAGTGTGTG TGTGTGTGTG	2900
TGTGTGTGTG GTGGGTTTCGT GCATGTATGT GTGCGTGTGT GTGTGTGTGT	2950
GTGTGTGTGT GTGTGTGTGC GTGTGTGTTT GTTTAGGGGT TTTTATAAAC	3000

AACTTTTTTTT	ATAAAGCAC	CTTTAGTTTA	CAATCTCTCT	TTATAACTGT	3050
TATAAATTTT	TAAACAACCC	AAAATGCGTT	CCATATAAAG	AAATGGCAAG	3100
TTATTTAGCT	ATCAAGATTT	TACATGTTTT	CTTTTAACTT	TTTTGTACAA	3150
TTGCATAGAC	GTGTAAAACC	TGCCATTGTT	AAJAAAACAA	TAACAGACTT	3200
AGAAACTACT	GAAATCTACA	GTATAGTACC	ACTACCCTTC	ACAAAAATAT	3250
AGATTTTATT	TCTTGTAAC	TCTTACTGTC	TAATCCTCTT	TGTTGTACGA	3300
ATATTATAAA	AACCATGCGG	GAATCAGGAG	TTGTAAAACA	TTTATTCTGC	3350
TCCTTCTTCA	TCTGTCATGA	CTGAACTAA	GGACTCCATC	GCTCTGCCCA	3400
AATCATCTGC	CATGTGAAA	AGGCTTCCTA	CATTGTGTCC	TCTCTCATTG	3450
GCTTTCCGGG	GGCATTTCTT	CCTCTTGAAC	TAGGGAAGGA	GTTGTTGAGT	3500
TGCTCCATCA	CTTCTTCTAA	CCCTGTGCTT	GTGTCCTGGG	GAGGACTCAG	3550
AAGATCTTCC	TCACCCATAG	ATTCTGAAGT	TTGACTGCCA	ACCACTCGGA	3600
GCAGCATAGG	CTGACTGCTA	TCTGACCTCT	GCAGAGAGGT	GGAAGGAGAG	3650
GACACCGTGG	TGCCATTAC	CTTAGCTTCA	GCCTGGGGCT	GCTCCAGGAG	3700
CTGTCTCAGT	CTATGTAAC	GAGACTCCAG	CTGTTTATTG	TGGTCTTCCA	3750
GGATTTGCAT	CCTGGCTTCC	AGGCGTCCTT	TGTGTTGGCG	CAGTAGCTTA	3800
GCCTCAGCAA	TGAGCTCAGC	ATCCCTGGGA	CTCTGAGGAG	AGGTGGGCAT	3850
CATCTCAGGA	GGAGATGGCA	GTGGAGACAG	GCCTTTATGC	TCATGCTGCT	3900
GCTTCAGGCG	ATCATATTCT	GCTTGCAGAT	TCCTGTTTTT	TTCCTCAAGA	3950
TCTGCTAGGA	TTCTCTCTAG	CTCCCCTCTT	TCCTCACTCT	CTAAGGAAAT	4000
CAAGATCTGG	GCAGGACTAC	GAGGCTGGCT	CAGGGGGGAG	TCCTGGTTCA	4050
AACTTTGGCA	GTAATGCTGG	ATTAACAAAT	GTTTCATCATC	TATGCTCTCA	4100
TTAGGAGAGA	TGCTATCATT	TAGATAAGAT	CCATTGCTGT	TTTCCATTTT	4150
TGCTAGCCTG	CTAGCATAAT	GTTCAATGCG	TGAATGAGTA	TCATCGTGTG	4200
AAAGCTGGGG	GGACGAGGCA	GGCGCAGAAT	CTACTGGCCA	GAAGTTGATC	4250
AGAGTAACGG	GAGTTTCCAT	GTTGTCCCCC	TCTAACACAG	TCTGCACTGG	4300

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GGAGTGCAAT ACTCTACCAT GGGGTAGTGC ATTTTATGGC CCTTTGCAAC	4450
TCGGCCAGAA AAAAAGCAAC TTTGGCAGAT GTLATAATTA AAATGCTTTA	4500
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CAGCCACACC ATAGACTGGG GTTCCAGGCG CATCCAGTCA AGGAAGAGAG	4650
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CTCGGCTCAA TGTTACTGCC CCCAAAGGAA GCAACTTCAC CCAACTGTCT	4750
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ACGGATCCTC CCTGTTCGTC CCGTATCATA AACATTGAGA AGCCAGTTGA	4950
GACACATATC CACACAGAGA GGGACATTGA CCAGATTGTT GTGCTCTTGC	5000
TCCAGACGAT CATAAATTGT AGTCAAACAG TTAATTATCT GCAGGATATC	5050
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ATTCTGCTTC	TGAACTGCTG	GGAAATCACC	ACCGATGGGT	GCCTGACGGC	6000
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TGGAGTCTTC	TAGGAGCTTC	TCCTTACGGG	AAGCGTCCTG	TAGGACATTG	6350
GCAGTTGTTT	CTGCTTCCGT	AATCCAGGAA	AGAACTTCT	CCAGGTCCAG	6400
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TTCTTGATTG	CTGGTTTTGT	TTTTCAAATT	CTGGGCAGCA	GTAATGAGTT	6900

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TTGATGATCA TTTCATTGAT GTCTTCCAGA TCACCCACCA TCACTCTCTG	7000
TGATTTTATA ACTCGATCAA GCAGAGACAG CCAGTCTGTA AGTTCTGTCC	7050
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CACTAGAGTA ACAGTCTGAC TGGCAGAGGC TCCAGTAGTG CTCAGTCCAG	7200
GGGCACGGTC AGGCTGCTTT GTCCTCAGCT CCCGAAGTAA ATGGTTTACA	7250
GCCTCCCACT CAGACCTCAG ATCTTCTAAC TTCCTCTTCA CTGGCTGAGT	7300
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TTATTTCTTC CCCAGTTGCA TTCAGTGTTT TGACAACAGC TTGACGCTGC	8000
CCAATGCCAT CCTGGAGTTC CTTAAGATAC CATTTGTATT TAGCATGTTT	8050
CCAGTTTTCA GGATTTTGTG TCTTTTTGAA AAAGTGTCA ACTTCATTCA	8100
GCCATTGATT AAATACCTTC ATATCATAAT GAAAGTGTG CCATTTTCA	8150
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TCAATCCGAC	CTGAGATTG	TTGCAAATTG	TCTTTTATAT	TCTTAAGAGA	8350
CTCCTCTTGC	TTAAAAAGAT	CTTCAAAATC	T.TAGCACAG	AGTTCAGGAG	8400
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TGAGTCTTCG	AAACTGAGCA	AAATTGCTCT	CAATTTGCCG	CCAGCGCTTG	8600
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GCAATTCACG	ATCAATTTCC	TTTAATTTTC	TTTCATCTCT	GGGTTCAGGT	8750
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AGCTGCTGTT	TTATCTTTAT	TTCTCTCGC	TTTCTCTCAT	CTGTGATTCT	8950
TTGTTGTAAG	TTGTCTCCTC	TTTGCAACAA	TTCATTTACA	GTACCCTCAT	9000
TGTCTTCACT	CATATCTTTA	TTGAAGTCTT	CCTCTTTCAG	ATTCACCCCC	9050
TGCTGAATTT	CAGCCTCCAG	TGGTTCAAGC	AATTTTGTGA	TATCTGAGTT	9100
AAACTGCTCC	AATTCCTTCA	AAGGAATGGA	GGCCTTTCCA	GTCTTAATTC	9150
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GTCACGTGTG	GAGTCCACCT	TTGGGCGCAT	GTCATTCATT	TCAGCCTTTA	9300
AACGCTTAAG	AATGTCTTCC	TTTTGTTGTG	GTTTCTTCTT	TTCAGACTCA	9350
TCTAAAAGTT	CATCTGCATG	AATGATCCAC	TTTGTGATTT	GTTCTATGTT	9400
CTGATCAAAG	GTTTCCATGT	GTTTCTGGTA	TTCCAACAAA	AGATTTAGCC	9450
ATTCTTCTAC	TCTGGAGGTG	ACAGCTATCC	AGTTACTGTT	CAGAAGACTC	9500

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CTCTCCTAAT TCTGTAACAC TCTTCAAGTG AGCCTTCTGT TTCTCAATCT	9600
CTTTTGTGAGT AGCCTTTCCC CAGGCAACTT CAGAATCCAA ATTACTTGGC	9650
ATTCCCTCAA CTGCTGATCT CTTTCGTCAAT TCCTATCTG TTGCTGCCAG	9700
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TTGTAATGCA ATTTCAAAGC TGTTACTCGT TCATCAAGCT CTTTGGGATT	9850
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CCACTTCAGA CTTGACTTCA CTCAGGCTTT TATACAAGTT CACACAATGA	9950
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GGCATCCTTC CCCTGGTTAT GTTTCTTCAT TTCTTCTAAA CTTATCTCAT	10200
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GCATCCACCT TGTCAGTGAT ATAAGCTGCC AACTGCTTGT CAATGAATTC	10300
AAGCGACTCC TGAATTAAGT GCAAGGACTT TTCAATTTCC TGGGCAGACT	10350
GGATACTCTG TTCAAGCAAC TTTTGTTTCC TCACAGCCTC TTCATGTAGT	10400
TCCCTCCAAC GAGAATTAAA CGTCTCAAGC TCCTCATTGA TCAGTTCATC	10450
CATGACTCCT CCATCTGTAA GAGTCTGTGC CAATAGACGA ATCTGATTG	10500
GGTTCTCCTC TGAATGATGC ATCAGATTTT CAAGAGATTG TAGCACTTCA	10550
GTGATTTCTT CAGGTCCTGC AGGAACATTT TCCATGGTTT TAAGTTTCAA	10600
TTCTACTTCA TTGAGCCACT TGTTTGCTTT CTCTAAATAT GACAATAACT	10650
CATGCCAACA TGCCCAAAC TCTTCCAAAG TTTTGCATTT TCCATTCAGC	10700
CTGGTGACA GCCATTGGTA GTTGGTGGTC AGAGTTTCAA GTTCCTTTTT	10750
TAAGGCCTCT TGTGCTGAGG GTGGAGCGTG AGCTATTACA CTATTTACAG	10800

TCTCAGTAAG	GAGTTTCACT	TTAGTTTCTT	TTTGTAGTGC	CTCTTCTTTA	10850
GCTCTCTTCA	TTTCTTCAAC	AGCAGTCTGT	AATTCATCTG	GAGTTTTATA	10900
TTCAAAATCT	CTCTCTAGAT	ATTCTTCTTC	AGCTTGTGTC	ATCCACTCAT	10950
GCATCTCTGA	TAGATCTTTT	TGGAGGCTTA	CGJTTTTATC	CAAACCTGCC	11000
TTTAAGGCTT	CCTTTCTGGT	GTAGACCTGG	CGGCATATGT	GATCCCACTG	11050
AGTGTTAAGC	TCTCTAAGTT	CTGTCTCCAG	TCTGGATGCA	AACTCAAGTT	11100
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AAACATCAAC	TTCAGCCATC	CATTTCTGTA	AGGTTTTTAT	GTGATTCTGA	11300
AATTTTCGAA	GTTTATTTCAT	ATGTTCTTCT	AGCTTTTGGC	AGCTTTCCAC	11350
CAACTGGGAG	GAAAGTTTCT	TCCAGTGCCC	CTCAATCTCT	TCAAATTCTG	11400
ACAGATATTT	CTGGCATATT	TCTGAAGGTG	CTTTCTTGGC	CATCTCCTTC	11450
ACAGTGTCAC	TCAGATAGTT	GAAGCCATTT	TGTTGCTCTT	TCAAAGAACT	11500
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GTCCTGATGC	TACTCATTTGT	CTCCTGATAG	CGCATTGGTG	GTAAAGTGTC	11650
AAAAATTGTC	TGTAGCTCTT	TCTCTTTGGC	CCTCACACCA	TCAAAGATGT	11700
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CCCTGTCCCT	TTTCTTTCAG	TTGTAGACTC	TGAATTTTTA	ATTGCTCAAT	11800
TTGAGGCTGA	AGAGCTGACA	ATCTGTTGAC	TTCATCCTTA	CAAATTTTTA	11850
ACTGGCTTTT	AATTGCTGTT	GGCTCTGATA	GGGTGGTAGA	CTGGGTTTTT	11900
AACAAGTTTT	CGGCAGTAGT	TGTCATCTGT	TCCAATTGTT	GTAGCTGATT	11950
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TCTTTTCGAT AGACTGCAA TTCAGAACTC TGTAATACAG CTTCTGAACG 12250
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AGTTCCTCTT GGGCATGTTT TACCATGATT TGTTCCCTTG TGGTCACCAT 12400
AGTTACCGTT TCCATTACAG TTGTCTGTGT TAGGGATGGT TGAGTGGTGG 12450
TGACAGCCTG TGAAATTTGT GCTGAACTCT TTTCAAGTTT TTGGGTTAAA 12500
TTGTCCCAAC GTTGTGCAA GTTTTCCATC CAGATTTCCA TCTTTTGAGT 12550
CACTGACTTA TTTTTCAGTG CCGAAAGTAG ATCTTGATTG AGTGAACCTA 12600
GTTTTTCCAT GGTGGGCTTT TTCTTTTCTA GATCTATTTT TAAAGTAGAT 12650
ATTTTGTGAA GACTTGACAT CATTTCATTT TGATCTTTAA AGCCACTTGT 12700
CTGAATGTTT TCATTGCAT CTTCTTTTTC TGAAAGCCAT GACTAAAAA 12750
GGCACTGTTT TTCAGTAAAA TGCTGCCATT TTAGAAGAAT ATCTTGTA 12800
ACAATCCAGC GGTCTTCAGT CCATCTGCAG ATATTTGCCC ATCGATCTCC 12850
CAGTACCTTA AGTTGTTCTT CCAAAGCAGC TGTTGCATGA TCACCGCTGG 12900
ATTCATCAAC CACTACTACC ATGTGAGTGA GCGAGTTGAC CCTGACCTGC 12950
TCCTGTTCTA GATCTTCTTG AAGCACCTTA TGTGTTGTA CTTGGCATT 13000
TAGATCTTCA AGATCAGGTC CAAAGGGCTC TTCCTCCATT TTCTTAGTTC 13050
TCTCTTCAGT TTTTGTTAAC CAGTCATCTA GTTCTTTTAA TTTCTGATTC 13100
TGGAGATCCA TTAGAACCTT GTGTAATTTG CTTTGTTTTT CCATGCTAGC 13150
TACCCTGAGA CATTCCTATC TTGAATTTAG GAGATTCATT TGTCTTGCA 13200
CTTCAGCTTC TTCATCTTCT GATAATTTCC CTTTTCCAAC TAGTTGACTT 13250
CCTAACTGTA GAACATTACC AACAGTCCT TGATGAGATG TCAGATCCAT 13300
CATGAATCCC TCATGAGCAT GAAACTGTTT TTTCACTTCT TCAACATCAT 13350
TTGAAATCTC TCCTTGTGCT CGCAATGTAT CCTCGGCAGA AAGAAGCCAT 13400

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CTCCATCAAT GAACTGTCAA GTGACTTGTC TCTGGGAGCT TCCAAATGCT 13500
GTGAAGGATA GGGGCTCTGT GTGGAATCAG AGGTGGCAAC ATAAGCAGCC 13550
TGTGTGAAGG CATAACTCTT GAATCGAGGC TTAGGAGATG AAGAAGTTTG 13600
TTCATAGCCC TGTGCTAGAC TGA CTGTGAGAG TAATGCATCT 13650
GGTGATGTAA TTGAAAATGT TCTTCTCTAG TTACTTTTGA AGATGTCCTG 13700
GGCAACATTT CCACTTCTTG AATGGCTTCA ATGCTCACTT GTTGTGGCAA 13750
AACTTGAAAG AGTGATGTGA TGTACATTAA GATGGACTTC TTGTCTGGAT 13800
AAGTGGTAGC AACATCTTCA GGATCAAGAA GTTTTTCTAT GCCTAACTGG 13850
CATTTTGCAA TGTTGAAGGC ATGTTCCAGT CTTTGGGTGG CTGAGTGCTG 13900
TGAAACCACA CTATTCCAAT CAAACAGGTC GGGCCTGTGA CTATGGATAA 13950
GAGCATTCAA AGCCAACCCG TCGGACCAGC TAGAGGTGAA GTTGATGACG 14000
TTAACCTGTG GATAATTACG TGTTGACTGT CGAACCAGC TCAGAAGAAT 14050
CTTTTCACTG TTGGTTTGCT GCAATCCAGC CATGATAGTT TTCATCACAT 14100
TTTTGACCTG CCAGTGGAGG ATTATATTCC AAATCAAACC AAGAGTGAGT 14150
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ATTATTTTTT TGTAAGACCC GCAGTGCCTT GTTGACATTG TTCAGGGCAT 14250
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TCCAAGAGGT CTAGGAGGCG TTTTCCATCC TGCAGGTCAC TGAAGAGGTT 14350
GTCTATGTGT TGCTTTCCAA ACTTAGAAAA TTGTGCATTT ATCCATTTTG 14400
TGAATGTTTT CTTTTGAACA TCTTCTCTTT CATAACAGTC CTCTACTTCT 14450
TCCCACCAA GCATTTGGAA GAAAAAGTAT ATATCAAGGC AGGGATAAAA 14500
ATCTTGGTAA AAGTTTCTCC CAGTTTTATT GCTCCAGGAG GCTTAGGTAC 14550
GATGAGAAGC CAATAAACTT CAGCAGCCTT GACAAAAAAA AAAAAAAAAA 14600
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TTACGACATT TTGGAAAGTC CCGTTGATTT TGGTGCCAAA ACAAACCTCCC 15100
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GGGGCGTACT TGGCATATGA TACACTTGAT GTACTGCCAA GTGGGCAGTT 15350
TACCGTAAAT ACTCCACCCA TTGACGTCAA TGGAAAGTCC CTATTGGCGT 15400
TACTATGGGA ACATACGTCA TTATTGACGT CAATGGGCGG GGGTCGTTGG 15450
GCGGTCAGCC AGGCGGGCCA TTTACCGTAA GTTATGTAAC GACCTGCAGG 15500
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AAAATTATTC AGATTTCAC TCTCTTATT CAGTTTCCC GCGAAAATGG 15600
CCAAATCTTA CTCGGTTACG CCCAAATTTA CTACAACATC CGCCTAAAAC 15650
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ACACTTCCGC CACACTACTA CGTCACCCGC CCCGTTCCCA CGCCCCGCGC 15800
CACGTCACAA ACTCCACCCC CTCATTATCA TATTGGCTTC AATCCAAAAT 15850
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CAATGATCAT CATGACAGAT CTGCGCGCGA TCGATATCAG CGCTTTAAAT 15950
TTGCGCATGC TAGCTATAGT TCTAGAGGTA CCGTTGTGA ACGTTAGCCG 16000

GCTACGTATA CTCCGGAATA TTAATAGGCC TAGGATGCAT ATGGCGGCCG 16050
GCCGCCTGCA GCTGGCGCCA TCGATACGCG TACGTCGCGA CCGCGGACAT 16100
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TATTTACACAC CGCATACGTC AAAGCAACCA TAGTACGCGC CCTGTAGCGG 16400
CGCATTAAAGC GCGGCGGGTG TGGTGGTTAC GCGCAGCGTG ACCGCTACAC 16450
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CCTTTGACGT TGGAGTCCAC GTTCTTTAAT AGTGGACTCT TGTTCCAAAC 16700
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TTTTGCCGAT TTCGGCCTAT TGGTTAAAAA ATGAGCTGAT TTAACAAAAA 16800
TTTAACGCGA ATTTTAACAA AATATTAACG TTTACAATTT TATGGTGCAC 16850
TCTCAGTACA ATCTGCTCTG ATGCCGCATA GTTAAGCCAG CCCCACACC 16900
CGCCAACACC CGCTGACGCG CCCTGACGGG CTTGTCTGCT CCCGGCATCC 16950
GCTTACAGAC AAGCTGTGAC CGTCTCCGGG AGCTGCATGT GTCAGAGGTT 17000
TTCACCGTCA TCACCGAAAC GCGCGAGACG AAAGGGCCTC GTGATACGCC 17050
TATTTTATA GGTAAATGTC ATGATAATAA TGGTTTCTTA GACGTCAGGT 17100
GGCACTTTTC GGGGAAATGT GCGCGGAACC CCTATTTGTT TATTTTTCTA 17150
AATACATTCA AATATGTATC CGCTCATGAG ACAATAACCC TGATAAATGC 17200
TTCAATAATA TTGAAAAGG AAGAGTATGA GTATTCAACA TTTCCGTGTC 17250
GCCCTTATTC CCTTTTTTGC GGCATTTTGC CTCCTGTTT TTGCTCACCC 17300

AGAAACGCTG GTGAAAGTAA AAGATGCTGA AGATCAGTTG GGTGCACGAG 17350
TGGGTTACAT CGAACTGGAT CTCAACAGCG GTAAGATCCT TGAGAGTTTT 17400
CGCCCCGAAG AACGTTTTCC AATGATGAGC ACTTTTAAAG TTCTGCTATG 17450
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CGCCTTGATC GTTGGGAACC GGAGCTGAAT GAAGCCATAC CAAACGACGA 17750
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AACTCTTTTT CCGAAGGTAA CTGGCTTCAG CAGAGCGCAG ATACCAAATA 18400
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CGGATAAGGC GCAGCGGTCG GGCTGAACGG GGGGTTCGTG CACACAGCCC 18600

AGCTTGGAGC	GAACGACCTA	CACCGAACTG	AGATACCTAC	AGCGTGAGCT	18650
ATGAGAAAGC	GCCACGCTTC	CCGAAGGGAG	AAAGGCGGAC	AGGTATCCGG	18700
TAAGCGGCAG	GGTCGGAACA	GGAGAGCGCA	CGAGGGAGCT	TCCAGGGGGA	18750
AACGCCTGGT	ATCTTTATAG	TCCTGTCGGG	TTACGCCACC	TCTGACTTGA	18800
GCGTCGATTT	TTGTGATGCT	CGTCAGGGGG	GCGGAGCCTA	TGGAAAAACG	18850
CCAGCAACGC	GGCCTTTTTA	CGGTTCTCTG	CCTTTTGCTG	GCCTTTTGCT	18900
CACATGTTCT	TTCCTGCGTT	ATCCCCTGAT	TCTGTGGATA	ACCGTATTAC	18950
CGCCTTTGAG	TGAGCTGATA	CCGCTCGCCG	CAGCCGAACG	ACCGAGCGCA	19000
GCGAGTCAGT	GAGCGAGGAA	GCGGAAGAGC	GCCCAATACG	CAAACCGCCT	19050
CTCCCCGCGC	GTTGGCCGAT	TCATTAATGC	AGCTGGCACG	ACAGGTTTCC	19100
CGACTGGAAA	GCGGGCAGTG	AGCGCAACGC	AATTAATGTG	AGTTAGCTCA	19150
CTCATTAGGC	ACCCCAGGCT	TTACACTTTA	TGCTTCCGGC	TCGTATGTTG	19200
TGTGGAATTG	TGAGCGGATA	ACAATTTTAC	ACAGGAAACA	GCTATGACCA	19250
TGATTACGAA	TTCGAATGGC	CATGGGACGT	CGACCTGAGG	TAATTATAAC	19300
CCGGGGCC					19307

WHAT IS CLAIMED IS:

1. A recombinant shuttle vector comprising:
 - (a) the DNA sequences of, or corresponding to, a portion of the genome of an adenovirus which comprises DNA sequences of, or corresponding to, the adenovirus 5' and 3' inverted terminal repeats and packaging/enhancer domain necessary for replication and virion encapsidation in the absence of sequence encoding viral genes;
 - (b) a selected gene operatively linked to regulatory sequences directing its expression, said gene operatively linked to the DNA of (a) and capable of expression in a target cell in vivo or in vitro.
2. The vector according to claim 1 wherein said DNA sequences (a) comprise the native adenovirus 5' inverted terminal repeats and packaging sequences.
3. The vector according to claim 1 wherein said DNA sequences (a) comprise the native adenovirus 3' inverted terminal repeat sequences.
4. The vector according to claim 1 wherein said selected gene (b) is a reporter gene.
5. The vector according to claim 4 wherein said reporter gene is selected from the group consisting of the genes encoding β -galactosidase, alkaline phosphatase and green fluorescent protein.
6. The vector according to claim 1 wherein said selected gene (b) is a therapeutic gene.

7. The vector according to claim 6 wherein said therapeutic gene is selected from the group consisting of a normal CFTR gene, a DMD Becker allele and a normal LDL gene.

8. A crippled adenovirus helper virus comprising a modified adenovirus sequence in place of native adenovirus sequence map units 0-1, which modification reduces the packaging efficiency of said virus, said virus also containing selected adenovirus genes necessary to direct a productive viral infection.

9. The helper virus according to claim 8 wherein said modified sequence comprises:

- i. a fragment of adenovirus map units 0-1;
- ii. a fragment of (i) containing a 5' inverted terminal repeat and between one to four selected packaging sequences,
- iii. a modified fragment of (i) containing at least one PAC consensus sequence in place of at least one native PAC sequence; and
- iv. a modified fragment of (ii), wherein said native PAC sequences are mutated to contain modified sequences.

10. The virus according to claim 8 wherein said modified sequence comprises Ad5 base pairs 1-269.

11. The virus according to claim 8 wherein said sequence (ii) comprises Ad5 base pairs 1-321.

12. The virus according to claim 8 wherein said helper adenovirus is conjugated to a poly-cation sequence.

13. A method for producing a recombinant adenovirus which comprises transfecting a selected host cell with

(a) a recombinant shuttle vector comprising

i. the DNA sequences of, or corresponding to, a portion of the genome of an adenovirus which comprises adenovirus 5' and 3' cis-elements necessary for replication and virion encapsidation in the absence of sequence encoding viral genes; and

ii. a selected gene operatively linked to regulatory sequences directing its expression, said gene linked to the DNA of (a) and capable of expression in a target cell in vivo or in vitro; and

(b) a helper adenovirus comprising sufficient adenovirus gene sequences necessary for a productive viral infection, wherein said transfected host cell permits the formation of a recombinant virus comprising the DNA of (i) and (ii) in an adenoviral capsid, and isolating and purifying the recombinant virus from said cell.

14. The method according to claim 13, wherein said helper virus is a crippled helper virus comprising a modified adenovirus sequence in place of native adenovirus sequence map units 0-1, which modification reduces the packaging efficiency of said helper virus, said helper virus also containing selected adenovirus genes necessary to direct a productive viral infection.

15. The method according to claim 13 wherein said helper adenovirus is associated with a poly-cation sequence.

16. The method according to claim 13 wherein said vector is associated with said helper adenovirus conjugate in a single particle.

17. The method according to claim 13 wherein said helper virus is an adenovirus sequence containing deletions of all or portions of the E1a and E1b genes.

18. The method according to claim 13 wherein said helper virus is an adenovirus sequence containing deletions of all or a portion of the E3 gene.

19. A recombinant adenovirus comprising

- i. the DNA of, or corresponding to, a portion of the genome of an adenovirus which comprises adenovirus 5' and 3' cis-elements necessary for replication and virion encapsidation in the absence of sequence encoding viral genes;
- ii. a selected gene operatively linked to regulatory sequences directing its expression, said gene linked to the DNA of (a) and capable of expression in a target cell *in vivo* or *in vitro*;
said DNA and gene encapsidated in an adenoviral capsid.

20. The virus according to claim 19 wherein said viral capsid is a capsid of an adenovirus serotype selected from the group consisting of types 2, 4, 5, 7, 12 and 40.

21. The virus according to claim 19 wherein said selected gene is a CFTR gene, a DMD gene and an LDL gene.

22. The use of a recombinant adenovirus according to claim 19 for the manufacture of a pharmaceutical composition suitable for delivering and integrating a selected gene into the chromosome of a target cell.

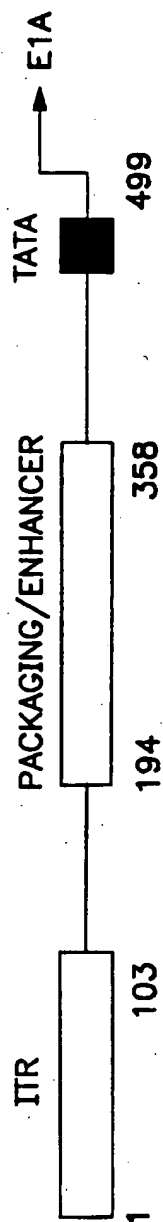


FIG. 1A

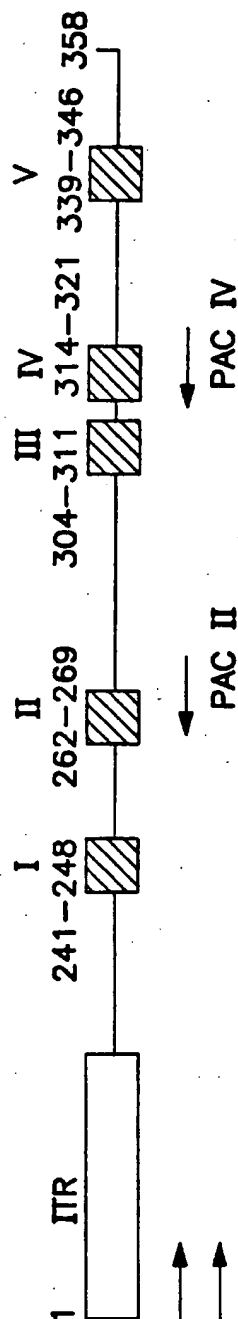
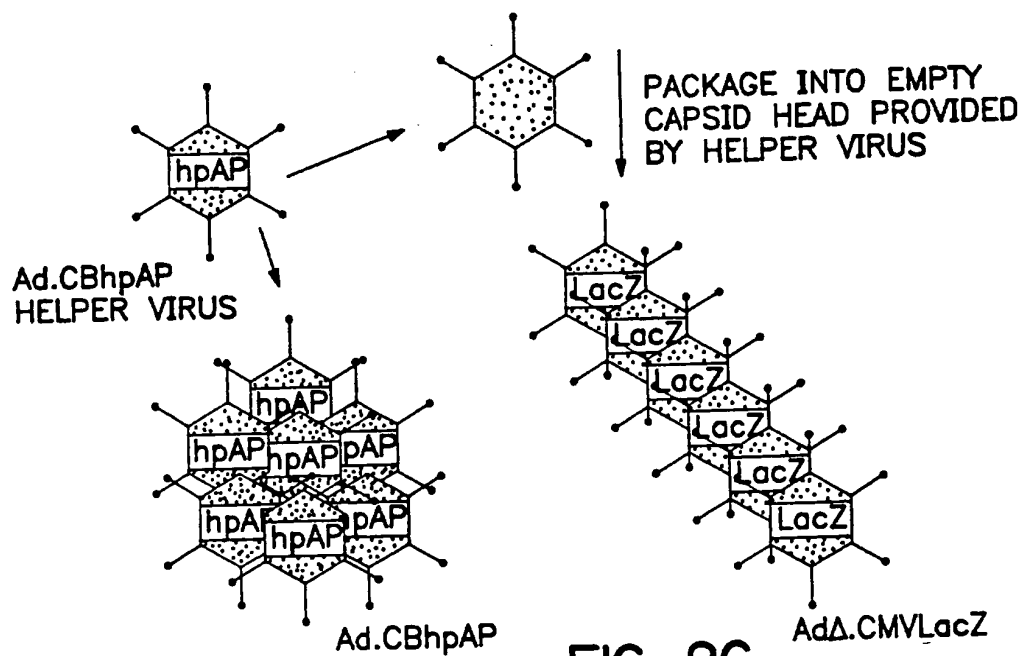
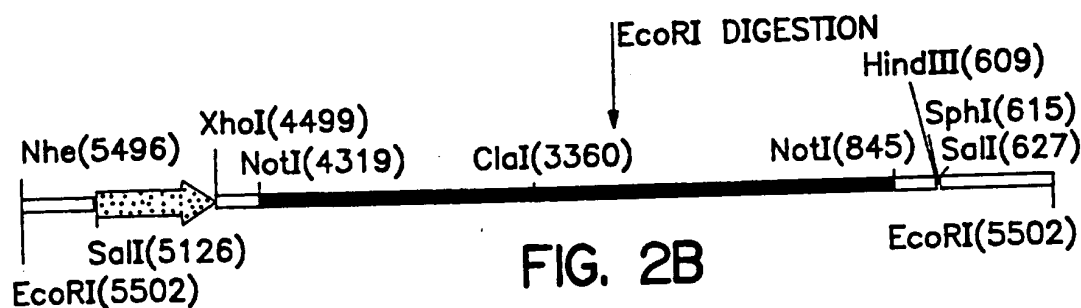
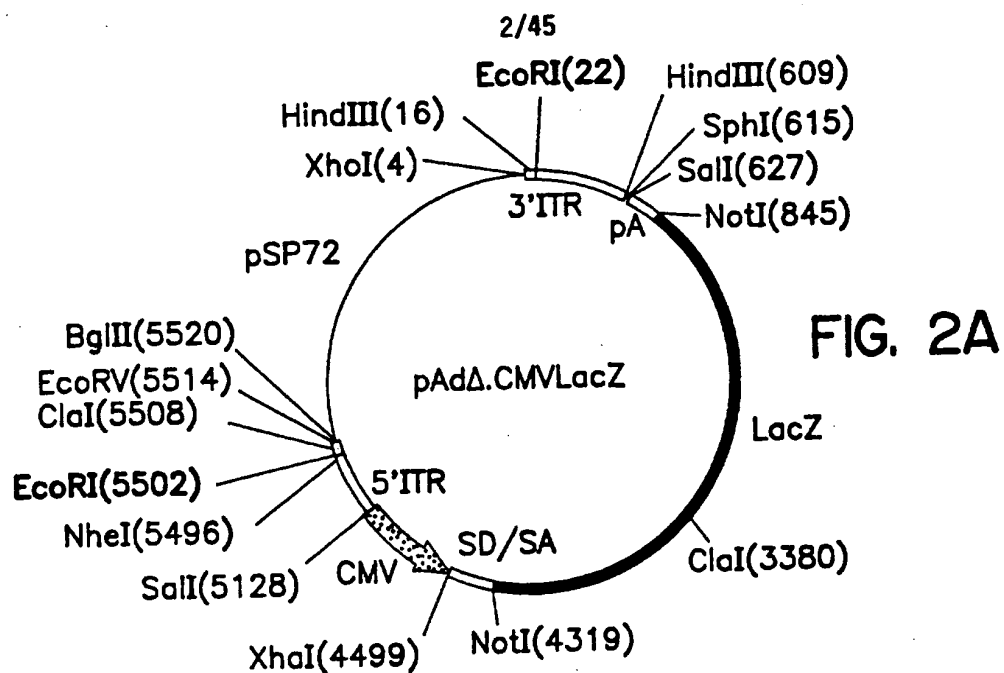


FIG. 1B



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FIGURE 3A

GAAC TCGAGC AGCTGAAGCT TGAATTCCAT CATCAATAAT ATACCTTATT	50
TTGGATTGAA GCCAATATGA TAATGAGGGG GTGGAGTTTG TGACGTGGCG	100
CGGGGCGTGG GAACGGGGCG GGTGACGTAG GTTTTAGGGC GGAGTAACTT	150
GTATGTGTTG GGAATTGTAG TTTTCTTAAA ATGGGAAGTT ACGTAACGTG	200
GGAAAACGGA AGTGACGATT TGAGGAAGTT GTGGGTTTTT TGGCTTTCGT	250
TTCTGGGCGT AGGTTCCGCT GCGGTTTTCT GGGTGTTTTT TGTGGACTTT	300
AACCGTTACG TCATTTTTTA GTCCTATATA TACTCGCTCT GCACTTGGCC	350
CTTTTTTACA CTGTGACTGA TTGAGCTGGT GCCGTGTCGA GTGGTGTTTT	400
TTTAATAGGT TTTCTTTTTT ACTGGTAAGG CTGACTGTTA GGCTGCCGCT	450
GTGAAGCGCT GTATGTTGTT CTGGAGCGGG AGGGTGCTAT TTTGCCTAGG	500
CAGGAGGGTT TTTCAGGTGT TTATGTGTTT TTCTCTCCTA TTAATTTTGT	550
TATACCTCCT ATGGGGGCTG TAATGTTGTC TCTACGCCTG CGGGTATGTA	600
TTCCCCCAA GCTTG CATGC CTGCAGGTCG ACTCTAGAGG ATCCGAAAAA	650
ACCTCCCACA CCTCCCCCTG AACCTGAAAC ATAAATGAA TGCAATTGTT	700
GTTGTAACT TGTTTATTGC AGCTTATAAT GGTTACAAAT AAAGCAATAG	750
CATCACAAAT TTCACAAATA AAGCATTTTT TCACTGCAT TCTAGTTGTG	800
GTTTGTCCAA ACTCATCAAT GTATCTTATC ATGTCTGGAT CCCC GCGGCC	850
GCCTAGAGTC GAGGCCGAGT TTGTCAGAAA GCAGACCAA CAGCGGTTGG	900
AATAATAGCG AGAACAGAGA AATAGCGGCA AAAATAATAC CCGTATCACT	950
TTTGCTGATA TGGTTGATGT CATGTAGCCA AATCGGGAAA AACGGGAAGT	1000
AGGCTCCCAT GATAAAAAAG TAAAAGAAAA AGAATAAACC GAACATCCAA	1050
AAGTTTGTGT TTTTTAAATA GTACATAATG GATTTCTTA CGCGAAATAC	1100
GGGCAGACAT GGCCTGCCCC GTTATTATTA TTTTGTGACAC CAGACCAACT	1150
GGTAATGGTA GCGACCGGCG CTCAGCTGTA ATTCCGCCGA TACTGACGGG	1200
CTCCAGGAGT CGTCGCCACC AATCCCCATA TGGAAACCGT CGATATTCAG	1250
CCATGTGCCT TCTTCGCGT GCAGCAGATG GCGATGGCTG CTTTCCATCA	1300
GTGCTGTTG ACTGTAGCGG CTGATGTTGA ACTGGAAGTC GCCGCGCCAC	1350

FIGURE 3B

TGGTGTGGGC CATAATTCAA TTCGCGCGTC CCGCAGCGCA GACCGTTTTTC	1400
GCTCGGGAAG ACGTACGGGG TATACATGTC TGACAATGGC AGATCCCAGC	1450
GGTCAAAACA GGCGGCAGTA AGGCGGTCGG GATAGTTTTTC TTGCGGCCCT	1500
AATCCGAGCC AGTTTACCCG CTCTGCTACC TGCGCCAGCT GGCAGTTCAG	1550
GCCAATCCGC GCCGGATGCG GTGTATCGCT CGCCACTTCA ACATCAACGG	1600
TAATCGCCAT TTGACCACTA CCATCAATCC GGTAGGTTTT CCGGCTGATA	1650
AATAAGGTTT TCCCCTGATG CTGCCACGCG TGAGCGGTCG TAATCAGCAC	1700
CGCATCAGCA AGTGTATCTG CCGTGCACTG CAACAACGCT GCTTCGGCCT	1750
GGTAATGGCC CGCCGCCTTC CAGCGTTCGA CCCAGGCGTT AGGGTCAATG	1800
CGGGTCGCTT CACTTACGCC AATGTCGTTA TCCAGCGGTG CACGGGTGAA	1850
CTGATCGCGC AGCGGCGTCA GCAGTTGTTT TTTATCGCCA ATCCACATCT	1900
GTGAAAGAAA GCCTGACTGG CGGTTAAATT GCCAACGCTT ATTACCCAGC	1950
TCGATGCAAA AATCCATTTT GCTGGTGGTC AGATGCGGGA TGGCGTGGGA	2000
CGCGGCGGGG AGCGTCACAC TGAGGTTTTTC CGCCAGACGC CACTGCTGCC	2050
AGGCGCTGAT GTGCCCCGGCT TCTGACCATG CGGTCGCGTT CGGTTGCACT	2100
ACGCGTACTG TGAGCCAGAG TTGCCCCGGC CTCTCCGGCT GCGGTAGTTC	2150
AGGCAGTTCA ATCAACTGTT TACCTTGTTG AGCGACATCC AGAGGCACTT	2200
CACCGCTTGC CAGCGGCTTA CCATCCAGCG CCACCATCCA GTGCAGGAGC	2250
TCGTTATCGC TATGACGGAA CAGGTATTCTG CTGGTCACTT CGATGGTTTG	2300
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GTTGCCGTTT TCATCATATT TAATCAGCGA CTGATCCACC CAGTCCCAGA	2500
CGAAGCCGCC CTGTAAACGG GGATACTGAC GAAACGCCTG CCAGTATTTA	2550
GCGAAACCGC CAAGACTGTT ACCCATCGCG TGGGCGTATT CGCAAAGGAT	2600
CAGCGGGCGC GTCTCTCCAG GTAGCGAAAG CCATTTTTTG ATGGACCATT	2650

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FIGURE 3C

TCGGCACAGC	CGGGAAGGGC	TGGTCTTCAT	CCACGCGCGC	GTACATCGGG	2700
CAAATAATAT	CGGTGGCCGT	GGTGTGGGCT	CCGCCGCCTT	CATACTGCAC	2750
CGGGCGGGAA	GGATCGACAG	ATTTGATCCA	GCGATACAGC	GCGTCGTGAT	2800
TAGCGCCGTG	GCCTGATTCA	TTCCCCAGCG	ACCAGATGAT	CACACTCGGG	2850
TGATTACGAT	CGCGCTGCAC	CATTCGCGTT	ACGCGTTCGC	TCATCGCCGG	2900
TAGCCAGCGC	GGATCATCGG	TCAGACGATT	CATTGGCACC	ATGCCGTGGG	2950
TTTCAATATT	GGCTTCATCC	ACCACATACA	GGCCGTAGCG	GTCGCACAGC	3000
GTGTACCACA	GCGGATGGTT	CGGATAATGC	GAACAGCGCA	CGGCGTTAAA	3050
GTTGTTCTGC	TTCATCAGCA	GGATATCCTG	CACCATCGTC	TGCTCATCCA	3100
TGACCTGACC	ATGCAGAGGA	TGATGCTCGT	GACGGTTAAC	GCCTCGAATC	3150
AGCAACGGCT	TGCCGTTTCA	CAGCAGCAGA	CCATTTTCAA	TCCGCACCTC	3200
GCGGAAACCG	ACATCGCAGG	CTTCTGCTTC	AATCAGCGTG	CCGTCGGCGG	3250
TGTGCAGTTC	AACCACCGCA	CGATAGAGAT	TCGGGATTTT	GGCGCTCCAC	3300
AGTTTCGGGT	TTTCGACGTT	CAGACGTAGT	GTGACGCGAT	CGGCATAACC	3350
ACCACGCTCA	TCGATAATTT	CACCGCCGAA	AGGCGCGGTG	CCGCTGGCGA	3400
CCTGCGTTTC	ACCCTGCCAT	AAAGAACTG	TTACCCGTAG	GTAGTCACGC	3450
AACTCGCCGC	ACATCTGAAC	TTCAGCCTCC	AGTACAGCGC	GGCTGAAATC	3500
ATCATTAAAG	CGAGTGGAAC	CATGGAAATC	GCTGATTTGT	GTAGTCGGTT	3550
TATGCAGCAA	CGAGACGTCA	CGGAAAATGC	CGCTCATCCG	CCACATATCC	3600
TGATCTTCCA	GATAACTGCC	GTCACCTCAA	CGCAGCACCA	TCACCGCGAG	3650
GCGGTTTTCT	CCGGCGCGTA	AAAATGCGCT	CAGGTCAAAT	TCAGACGGCA	3700
AACGACTGTC	CTGGCCGTAA	CCGACCCAGC	GCCCGTTGCA	CCACAGATGA	3750
AACGCCGAGT	TAACGCCATC	AAAAATAATT	CGCGTCTGGC	CTTCCTGTAG	3800
CCAGCTTTCA	TCAACATTAA	ATGTGAGCGA	GTAACAACCC	GTCGGATTCT	3850
CCGTGGGAAC	AAACGGCGGA	TTGACCGTAA	TGGGATAGGT	TACGTTGGTG	3900
TAGATGGGCG	CATCGTAACC	GTGCATCTGC	CAGTTTGAGG	GGACGACGAC	3950

FIGURE 3D

AGTATCGGCC TCAGGAAGAT CGCACTCCAG CCAGCTTTCC GGCACCGCTT	4000
CTGGTGCCGG AAACCAGGCA AAGCGCCATT CGCCATTGAG GCTGCGCAAC	4050
TGTTGGGAAG GCGGATCGGT GCGGGCCTCT TCCTATTAC GCCAGCTGGC	4100
CAAAGGGGGA TGTGCTGCAA GGCGATTAAG TTGGGTAACG CCAGGGTTTT	4150
CCCAGTCACG ACGTTGTAAA ACGACGGGAT CGCGCTTGAG CAGCTCCTTG	4200
CTGGTGTCCA GACCAATGCC TCCCAGACCG GCAACGAAAA TCACGTTCTT	4250
GTTGGTCAAA GTAAACGACA TGGTGACTTC TTTTTTGCTT TAGCAGGCTC	4300
TTTCGATCCC CGGGAATTGC GGCCGCGGGT ACAATTCCGC AGCTTTTAGA	4350
GCAGAAGTAA CACTTCCGTA CAGGCCTAGA AGTAAAGGCA ACATCCACTG	4400
AGGAGCAGTT CTTTGATTG CACCACCACC GGATCCGGGA CCTGAAATAA	4450
AAGACAAAAA GACTAAACTT ACCAGTTAAC TTTCTGGTTT TTCAGTTCCT	4500
CGAGTACCGG ATCCTCTAGA GTCCGGAGGC TGGATCGGTC CCGGTCTCTT	4550
CTATGGAGGT CAAAACAGCG TGGATGGCGT CTCCAGGCGA TCTGACGGTT	4600
CACTAAACGA GCTCTGCTTA TATAGACCTC CCACCGTACA CGCCTACCGC	4650
CCATTTGCGT CAATGGGGCG GAGTTGTTAC GACATTTTGG AAAGTCCCGT	4700
TGATTTTGGT GCCAAAACAA ACTCCCATG ACGTCAATGG GGTGGAGACT	4750
TGGAAATCCC CGTGAGTCAA ACCGCTATCC ACGCCCATG ATGTACTGCC	4800
AAAACCGCAT CACCATGGTA ATAGCGATGA CTAATACGTA GATGTACTGC	4850
CAAGTAGGAA AGTCCCATAA GGTCATGTAC TGGGCATAAT GCCAGGCGGG	4900
CCATTTACCG TCATTGACGT CAATAGGGGG CGTACTTGGC ATATGATACA	4950
CTTGATGTAC TGCCAAGTGG GCAGTTTACC GTAAATACTC CACCCATTGA	5000
CGTCAATGGA AAGTCCCTAT TGGCGTTACT ATGGGAACAT ACGTCATTAT	5050
TGACGTCAAT GGGCGGGGGT CGTTGGGCGG TCAGCCAGGC GGGCCATTTA	5100
CCGTAAGTTA TGTAACGACC TGCAGGTCGA CTCTAGAGGA TCTCCCTAGA	5150
CAAATATTAC GCGCTATGAG TAACACAAAA TTATTCAGAT TTCACTTCCT	5200
CTTATTCAGT TTTCCCGCGA AAATGGCCAA ATCTTACTCG GTTACGCCCA	5250

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FIGURE 3E

AATTTACTAC AACATCCGCC TAAAACCGCG CGAAAATTGT CACTTCCTGT	5300
GTACACCGGC GCACACCAA AACGTCACCT TTGCCACATC CGTCGCTTAC	5350
ATGTGTTCCG CCACACTTGC AACATCACAC TTCCGCCACA CTACTACGTC	5400
ACCCGCCCCG TTCCCACGCC CCGCGCCACG TCACAAACTC CACCCCCTCA	5450
TTATCATATT GGCTTCAATC CAAAATAAGG TATATTATTG ATGATGCTAG	5500
CGAATTCATC GATGATATCA GATCTGCCGG TCTCCCTATA GTGAGTCGTA	5550
TTAATTTCGA TAAGCCAGGT TAACCTGCAT TAATGAATCG GCCAACGCGC	5600
GGGGAGAGGC GGTTTGCGTA TTGGGCGCTC TTCCGCTTCC TCGCTCACTG	5650
ACTCGCTGCG CTCGGTCGTT CGGCTGCGGC GAGCGGTATC AGCTCACTCA	5700
AAGGCGGTAA TACGGTTATC CACAGAATCA GGGGATAACG CAGGAAAGAA	5750
CATGTGAGCA AAAGGCCAGC AAAAGGCCAG GAACCGTAAA AAGGCCGCGT	5800
TGCTGGCGTT TTTCCATAGG CTCCGCCCCC CTGACGAGCA TCACAAAAAT	5850
CGACGCTCAA GTCAGAGGTG GCGAAACCCG ACAGGACTAT AAAGATACCA	5900
GGCGTTTCCC CCTGGAAGCT CCCTCGTGCG CTCTCCTGTT CCGACCCTGC	5950
CGCTTACCGG ATACCTGTCC GCCTTTCTCC CTTCCGGAAG CGTGGCGCTT	6000
TCTCAATGCT CACGCTGTAG GTATCTCAGT TCGGTGTAGG TCGTTCGCTC	6050
CAAGCTGGGC TGTGTGCACG AACCCCCCGT TCAGCCCGAC CGCTGCGCCT	6100
TATCCGGTAA CTATCGTCTT GAGTCCAACC CGGTAAGACA CGACTTATCG	6150
CCACTGGCAG CAGCCACTGG TAACAGGATT AGCAGAGCGA GGTATGTAGG	6200
CGGTGCTACA GAGTTCTTGA AGTGGTGGCC TAACTACGGC TACACTAGAA	6250
GGACAGTATT TGGTATCTGC GCTCTGCTGA AGCCAGTTAC CTTCCGAAAA	6300
AGAGTTGGTA GCTCTTGATC CGGCAAACAA ACCACCGCTG CTAGCGGTGG	6350
TTTTTTTGTT TGCAAGCAGC AGATTACGCG CAGAAAAAAA GGATCTCAAG	6400
AAGATCCTTT GATCTTTTCT ACGGGTCTG ACGCTCAGTG GAACGAAAC	6450
TCACGTTAAG GGATTTTGGT CATGAGATTA TCAAAAAGGA TCTTCACCTA	6500
GATCCTTTTA AATTAAAAAT GAAGTTTAA ATCAATCTAA AGTATATATG	6550

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FIGURE 3F

AGTAACTTG GTCTGACAGT TACCAATGCT TAATCAGTGA GGCACCTATC	6600
TCAGCGATCT GTCTATTTTCG TTCATCCATA GTTGCCTGAC TCCCCGTCGT	6650
GTAGATAACT ACGATACGGG AGGGCTTACC ATCTGGCCCC AGTGCTGCAA	6700
TGATACCGCG AGACCCACGC TCACCGGCTC C/GATTTATC AGCAATAAAC	6750
CAGCCAGCCG GAAGGGCCGA GCGCAGAAGT GGTCTGCAA CTTTATCCGC	6800
CTCCATCCAG TCTATTAATT GTTGCCGGGA AGCTAGAGTA AGTAGTTCGC	6850
CAGTTAATAG TTTGCGCAAC GTTGTTGCCA TTGCTACAGG CATCGTGGTG	6900
TCACGCTCGT CGTTTGGTAT GGCTTCATTC AGCTCCGGTT CCCAACGATC	6950
AAGGCGAGTT ACATGATCCC CCATGTTGTG CAAAAAGCG GTTAGCTCCT	7000
TCGGTCCTCC GATCGTTGTC AGAAGTAAGT TGGCCGCAGT GTTATCACTC	7050
ATGTTTATGG CAGCACTGCA TAATTCTCTT ACTGTCATGC CATCCGTAAG	7100
ATGCTTTTCT GTGACTGGTG AGTACTCAAC CAAGTCATTC TGAGAATAGT	7150
GTATGCGGCG ACCGAGTTGC TCTTGCCCGG CGTCAATACG GGATAATACC	7200
GCGCCACATA GCAGAACTTT AAAAGTGCTC ATCATTGGAA AACGTTCTTC	7250
GGGGCGAAAA CTCTCAAGGA TCTTACCGCT GTTGAGATCC AGTTCGATGT	7300
AACCCACTCG TGCACCCAAC TGATCTTCAG CATCTTTTAC TTTCACCAGC	7350
GTTTCTGGGT GAGCAAAAAC AGGAAGGCAA AATGCCGCAA AAAAGGGAAT	7400
AAGGGCGACA CGGAAATGTT GAATACTCAT ACTCTTCCTT TTTCAATATT	7450
ATTGAAGCAT TTATCAGGGT TATTGTCTCA TGAGCGGATA CATATTTGAA	7500
TGTATTTAGA AAAATAAACA AATAGGGGTT CCGCGCACAT TTCCCCGAAA	7550
AGTGCCACCT GACGTCTAAG AAACCATTAT TATCATGACA TTAACCTATA	7600
AAAATAGGCG TATCAGGAGG CCCTTTCGTC TCGCGCGTTT CGGTGATGAC	7650
GGTGA AAAACC TCTGACACAT GCAGCTCCCG GAGACGGTCA CAGCTTGTCT	7700
GTAAGCGGAT GCCGGGAGCA GACAAGCCCG TCAGGGCGCG TCAGCGGGTG	7750
TTGGCGGGTG TCGGGGCTGG CTTAACTATG CGGCATCAGA GCAGATTGTA	7800
CTGAGAGTGC ACCATATGGA CATATTGTCG TTAGAACGCG GCTACAATTA	7850
ATACATAACC TTATGTATCA TACACATACG ATTTAGGTGA CACTATA	7897

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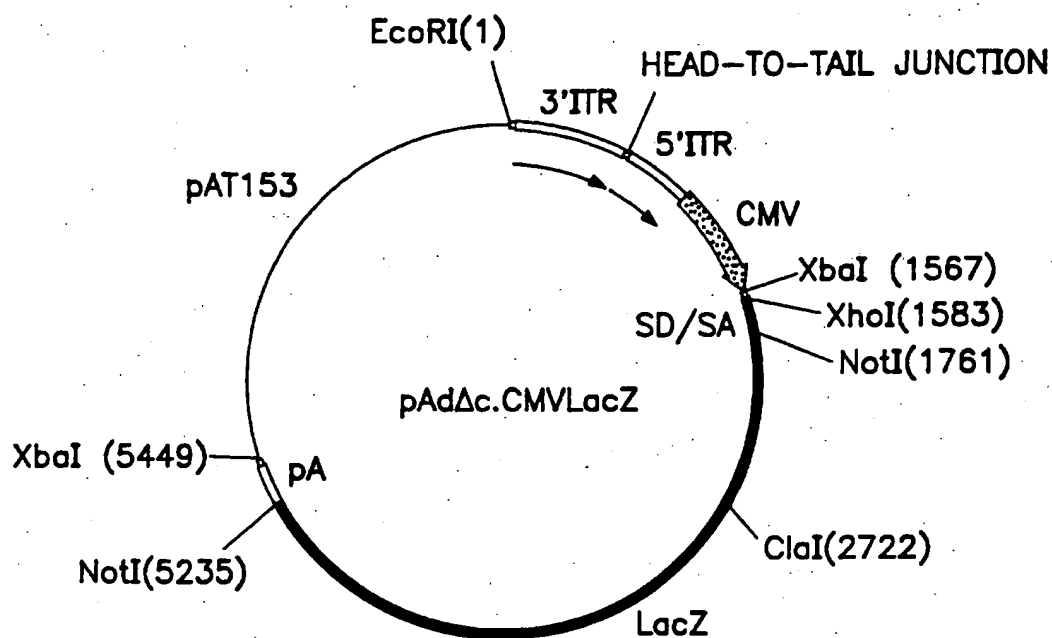


FIG. 4A

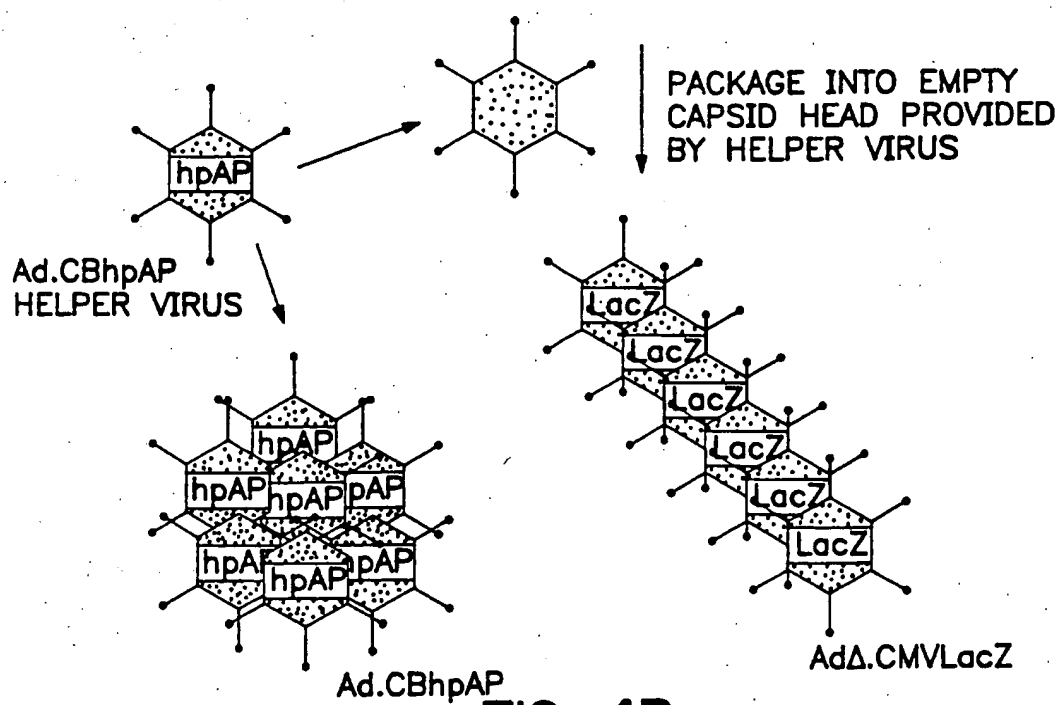


FIG. 4B

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FIGURE 5A

GAATTCGCTA GCTAGCGGGG GAATACATAC CCGCAGGCGT AGAGACAACA	50
TTACAGCCCC CATAGGAGGT ATAACAAAAT TAATAGGAGA GAAAAACACA	100
TAAACACCTG AAAAACCCTC CTGCCTAGGC AAAATAGCAC CCTCCCGCTC	150
CAGAACAACA TACAGCGCTT CACAGCGGCA GCCTAACAGT CAGCCTTACC	200
AGTAAAAAAG AAAACCTATT AAAAAAACAC CACTCGACAC GGCACCAGCT	250
CAATCAGTCA CAGTGTAATA AAGGGCCAAG TGCAGAGCGA GTATATATAG	300
GACTAAAAAA TGACGTAACG GTTAAAGTCC AAAAAAACA CCCAGAAAAC	350
CGCACGCGAA CCTACGCCCA GAAACGAAAG CAAAAAACC CACAACTTCC	400
TCAAATCGTC ACTTCCGTTT TCCCACGTTA CGTAACTTCC CATTTTAAGA	450
AAACTACAAT TCCCAACACA TACAAGTTAC TCCGCCCTAA AACCTACGTC	500
ACCCGCCCCG TTCCCACGCC CCGCGCCACG TCACAACTC CACCCCCTCA	550
TTATCATATT GGCTTCAATC CAAAATAAGG TATATTATTG ATGATGCTAG	600
CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG	650
GGGGTGGAGT TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG	700
TAGTAGTGTG GCGGAAGTGT GATGTTGCAA GTGTGGCGGA ACACATGTAA	750
GCGACGGATG TGGCAAAAGT GACGTTTTTG GTGTGCGCCG GTGTACACAG	800
GAAGTGACAA TTTTCGCGCG GTTTTAGGCG GATGTTGTAG TAAATTTGGG	850
CGTAACCGAG TAAGATTTGG CCATTTTCGC GGGAAACTG AATAAGAGGA	900
AGTGAAATCT GAATAATTTT GTGTTACTCA TAGCGCGTAA TATTTGTCTA	950
GGGAGATCAG CCTGCAGGTC GTTACATAAC TTACGGTAAA TGGCCCGCCT	1000
GGCTGACCGC CCAACGACCC CCGCCCATTG ACGTCAATAA TGACGTATGT	1050
TCCCATAGTA ACGCCAATAG GGACTTTCCA TTGACGTCAA TGGGTGGAGT	1100
ATTTACGGTA AACTGCCCCAC TTGGCAGTAC ATCAAGTGTA TCATATGCCA	1150
AGTACGCCCC CTATTGACGT CAATGACGGT AAATGGCCCC CCTGGCATTG	1200
TGCCCCAGTAC ATGACCTTAT GGGACTTTCC TACTTGGCAG TACATCTACG	1250
TATTAGTCAT CGCTATTACC ATGGTGATGC GGTTTTGGCA GTACATCAAT	1300

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FIGURE 5B

GGGCGTGGAT	AGCGGTTTGA	CTCACGGGGA	TTTCCAAGTC	TCCACCCCAT	1350
TGACGTCAAT	GGGAGTTTGT	TTTGGCACCA	AAATCAACGG	GACTTTTCCAA	1400
AATGTCGTAA	CAACTCCGCC	CCATTGACGC	AAATGGGCGG	TAGGCGTGTA	1450
CGGTGGGAGG	TCTATATAAG	CAGAGCTCGT	TTAGTGAACC	GTCAGATCGC	1500
CTGGAGACGC	CATCCACGCT	GTTTTGACCT	CCATAGAAGA	CACCGGGACC	1550
GATCCAGCCT	CCGGACTCTA	GAGGATCCGG	TACTCGAGGA	ACTGAAAAAC	1600
CAGAAAGTTA	ACTGGTAAGT	TTAGTCTTTT	TGTCTTTTAT	TTCAGGTCCC	1650
GGATCCGGTG	GTGGTGCAAA	TCAAAGAACT	GCTCCTCAGT	GGATGTTGCC	1700
TTTACTTCTA	GGCCTGTACG	GAAGTGTTAC	TTCTGCTCTA	AAAGCTGCGG	1750
AATTGTACCC	GCGGCCGCAA	TTCCCGGGGA	TCGAAAGAGC	CTGCTAAAGC	1800
AAAAAAGAAG	TCACCATGTC	GTTTACTTTG	ACCAACAAGA	ACGTGATTTT	1850
CGTTGCCGGT	CTGGGAGGCA	TTGGTCTGGA	CACCAGCAAG	GAGCTGCTCA	1900
AGCGCGATCC	CGTCGTTTTA	CAACGTCGTG	ACTGGGAAAA	CCCTGGCGTT	1950
ACCCAACTTA	ATCGCCTTGC	AGCACATCCC	CCTTTCGCCA	GCTGGCGTAA	2000
TAGCGAAGAG	GCCCGCACCG	ATCGCCCTTC	CCAACAGTTG	CGCAGCCTGA	2050
ATGGCGAATG	GCGCTTTGCC	TGGTTTCCGG	CACCAGAAGC	GGTGCCGGAA	2100
AGCTGGCTGG	AGTGCGATCT	TCCTGAGGCC	GATACTGTCG	TCGTCCCCTC	2150
AAACTGGCAG	ATGCACGGTT	ACGATGCGCC	CATCTACACC	AACGTAACCT	2200
ATCCCATTAC	GGTCAATCCG	CCGTTTGTTT	CCACGGAGAA	TCCGACGGGT	2250
TGTTACTCGC	TCACATTTAA	TGTTGATGAA	AGCTGGCTAC	AGGAAGGCCA	2300
GACGCGAATT	ATTTTTGATG	GCGTTAACTC	GGCGTTTCAT	CTCTGGTGCA	2350
ACGGGCGCTG	GGTCGGTTAC	GGCCAGGACA	GTCGTTTGCC	GTCTGAATTT	2400
GACCTGAGCG	CATTTTTTACG	CGCCGGAGAA	AACCGCCTCG	CGGTGATGGT	2450
GCTGCGTTGG	AGTGACGGCA	GTTATCTGGA	AGATCAGGAT	ATGTGGCGGA	2500
TGAGCGGCAT	TTCCCGTGAC	GTCTCGTTGC	TGCATAAACC	GA CTACACAA	2550
ATCAGCGATT	TCCATGTTGC	CACTCGCTTT	AATGATGATT	TCAGCCGCGC	2600

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FIGURE 5C

TGTACTGGAG GCTGAAGTTC AGATGTGCGG CGAGTTGCGT GACTACCTAC	2650
GGGTAACAGT TTCTTTATGG CAGGGTGAAA CGCAGGTCGC CAGCGGCACC	2700
GCGCCTTTTCG GCGGTGAAAT TATCGATGAG CGTGGTGGTT ATGCCGATCG	2750
CGTCACACTA CGTCTGAACG TCGAAAACCC GAAACTGTGG AGCGCCGAAA	2800
TCCCGAATCT CTATCGTGCG GTGGTTGAAC TGCACACCGC CGACGGCACG	2850
CTGATTGAAG CAGAAGCCTG CGATGTGCGT TTCCGCGAGG TCGCGATTGA	2900
AAATGGTCTG CTGCTGCTGA ACGGCAAGCC GTTGCTGATT CGAGGCGTTA	2950
ACCGTCACGA GCATCATCCT CTGCATGGTC AGGTCATGGA TGAGCAGACC	3000
ATGGTGCAGG ATATCCTGCT GATGAAGCAG AACAACTTTA ACGCCGTGCG	3050
CTGTTTCGCAT TATCCGAACC ATCCGCTGTG GTACACGCTG TCGGACCGCT	3100
ACGGCCTGTA TGTGGTGGAT GAAGCCAATA TTGAAACCCA CGGCATGGTG	3150
CCAATGAATC GTCTGACCGA TGATCCGCGC TGGCTACCGG CGATGAGCGA	3200
ACGCGTAACG CGAATGGTGC AGCGCGATCG TAATCACCCG AGTGTGATCA	3250
TCTGCTCGCT GGGGAATGAA TCAGGCCACG GCGCTAATCA CGACGCGCTG	3300
TATCGCTGGA TCAAATCTGT CGATCCTTCC CGCCCGGTGC AGTATGAAGG	3350
CGGCGGAGCC GACACCACGG CCACCGATAT TATTTGCCCC ATGTACGCGC	3400
GCGTGGATGA AGACCAGCCC TTCCCGGCTG TGCCGAAATG GTCCATCAAA	3450
AAATGGCTTT CGCTACCTGG AGAGACGCGC CCGCTGATCC TTTGCGAATA	3500
CGCCCACGCG ATGGGTAACA GTCTTGGCGG TTTCGCTAAA TACTGGCAGG	3550
CGTTTCGTCA GTATCCCCGT TTACAGGGCG GCTTCGTCTG GGAAGGCTG	3600
GATCAGTCGC TGATTAAATA TGATGAAAAC GGCAACCCGT GGTCGGCTTA	3650
CGGCGGTGAT TTTGGCGATA CGCCGAACGA TCGCCAGTTC TGTATGAACG	3700
GTCTGGTCTT TGCCGACCGC ACGCCGCATC CAGCGCTGAC GGAAGCAAAA	3750
CACCAGCAGC AGTTTTTCCA GTTCCGTTTA TCCGGGCAAA CCATCGAAGT	3800
GACCAGCGAA TACCTGTTCC GTCATAGCGA TAACGAGCTC CTGCACTGGA	3850
TGGTGGCGCT GGATGGTAAG CCGCTGGCAA GCGGTGAAGT GCCTCTGGAT	3900

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FIGURE 5D

GTCGCTCCAC AAGGTAAACA GTTGATTGAA CTGCCTGAAC TACCGCAGCC	3950
GGAGAGCGCC GGGCAACTCT GGCTCACAGT ACGCGTAGTG CAACCGAACG	4000
CGACCGCATG GTCAGAAGCC GGGCACATCA GCGCCTGGCA GCAGTGGCGT	4050
CTGGCGGAAA ACCTCAGTGT GACGCTCCCC GCGCGTCCC ACGCCATCCC	4100
GCATCTGACC ACCAGCGAAA TGGATTTTGT CATCGAGCTG GGTAATAAGC	4150
GTTGGCAATT TAACCGCCAG TCAGGCTTTC TTTCACAGAT GTGGATTGGC	4200
GATAAAAAAC AACTGCTGAC GCCGCTGCGC GATCAGTTCA CCCGTGCACC	4250
GCTGGATAAC GACATTGGCG TAAGTGAAGC GACCCGCATT GACCCTAACG	4300
CCTGGGTCGA ACGCTGGAAG GCGGCGGGCC ATTACCAGGC CGAAGCAGCG	4350
TTGTTGCAGT GCACGGCAGA TACACTTGCT GATGCGGTGC TGATTACGAC	4400
CGCTCACGCG TGGCAGCATC AGGGGAAAAC CTTATTTATC AGCCGGAAAA	4450
CCTACCGGAT TGATGGTAGT GGTCAAATGG CGATTACCGT TGATGTTGAA	4500
GTGGCGAGCG ATACACCGCA TCCGGCGCGG ATTGGCCTGA ACTGCCAGCT	4550
GGCGCAGGTA GCAGAGCGGG TAAACTGGCT CGGATTAGGG CCGCAAGAAA	4600
ACTATCCCGA CCGCCTTACT GCCGCCTGTT TTGACCGCTG GGATCTGCCA	4650
TTGTCAGACA TGTATACCCC GTACGTCTTC CCGAGCGAAA ACGGTCTGCG	4700
CTGCGGGACG CGCGAATTGA ATTATGGCCC ACACCAGTGG CGCGGCGACT	4750
TCCAGTTCAA CATCAGCCGC TACAGTCAAC AGCAACTGAT GGAAACCAGC	4800
CATCGCCATC TGCTGCACGC GGAAGAAGGC ACATGGCTGA ATATCGACGG	4850
TTTCCATATG GGGATTGGTG GCGACGACTC CTGGAGCCCG TCAGTATCGG	4900
CGGAATTACA GCTGAGCGCC GGTGCTACC ATTACCAGTT GGTCTGGTGT	4950
CAAAAATAAT AATAACCGGG CAGGCCATGT CTGCCCCTAT TTCGCGTAAG	5000
GAAATCCATT ATGTACTATT TAAAAACAC AAACTTTTGG ATGTTGCGTT	5050
TATTCTTTTT CTTTTACTTT TTTATCATGG GAGCCTACTT CCCGTTTTTC	5100
CCGATTGGC TACATGACAT CAACCATATC AGCAAAAGTG ATACGGGTAT	5150
TATTTTGGC GCTATTTCTC TGTTCTCGCT ATTATTCCAA CCGCTGTTTG	5200
GTCTGCTTTC TGACAAACTC GGCCTCGACT CTAGGCGGCC GCGGGGATCC	5250

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FIGURE 5E

AGACATGATA AGATACATTG ATGAGTTTGG ACAAACCACA ACTAGAATGC	5300
AGTGAAAAAA ATGCTTTATT TGTGAAATTT GTGATGCTAT TGCTTTATTT	5350
GTAACCATTA TAAGCTGCAA TAAACAAGTT AACAAACAACA ATTGCATTCA	5400
TTTTATGTTT CAGGTTTCAGG GGGAGGTGTG GGAGGTTTTT TCGGATCCTC	5450
TAGAGTCGAC GACGCGAGGC TGGATGGCCT TCCCCATTAT GATTCTTCTC	5500
GCTTCCGGCG GCATCGGGAT GCCCGCGTTG CAGGCCATGC TGTCCAGGCA	5550
GGTAGATGAC GACCATCAGG GACAGCTTCA AGGATCGCTC GCGGCTCTTA	5600
CCAGCCTAAC TTCGATCACT GGACCGCTGA TCGTCACGGC GATTTATGCC	5650
GCCTCGGCGA GCACATGGAA CGGGTTGGCA TGGATTGTAG GCGCCGCCCT	5700
ATACCTTGTC TGCCTCCCCG CGTTGCGTCG CGGTGCATGG AGCCGGGCCA	5750
CCTCGACCTG AATGGAAGCC GCGGCGACCT CGCTAACGGA TTCACCACTC	5800
CAAGAATTGG AGCCAATCAA TTCTTGCGGA GAACTGTGAA TGCGCAAACC	5850
AACCCTTGGC AGAACATATC CATCGCGTCC GCCATCTCCA GCAGCCGCAC	5900
GCGGCGCATC TCGGGCAGCG TTGGGTCCTG GCCACGGGTG CGCATGATCG	5950
TGCTCCTGTC GTTGAGGACC CGGCTAGGCT GGCGGGGTTG CCTTACTGGT	6000
TAGCAGAATG AATCACCGAT ACGCGAGCGA ACGTGAAGCG ACTGCTGCTG	6050
CAAAACGTCT GCGACCTGAG CAACAACATG AATGGTCTTC GGTTCCTGTG	6100
TTTCGTAAAG TCTGGAAACG CGGAAGTCAG CGCCCTGCAC CATTATGTTC	6150
CGGATCTGCA TCGCAGGATG CTGCTGGCTA CCCTGTGGAA CACCTACATC	6200
TGTATTAACG AAGCCTTTCT CAATGCTCAC GCTGTAGGTA TCTCAGTTCTG	6250
GTGTAGGTCG TTCGCTCCAA GCTGGGCTGT GTGCACGAAC CCCCCGTTCA	6300
GCCCCGACCGC TGCGCCTTAT CCGGTAACCTA TCGTCTTGAG TCCAACCCGG	6350
TAAGACACGA CTTATCGCCA CTGGCAGCAG CCACTGGTAA CAGGATTAGC	6400
AGAGCGAGGT ATGTAGGCGG TGCTACAGAG TTCTTGAAGT GGTGGCCTAA	6450
CTACGGCTAC ACTAGAAGGA CAGTATTTGG TATCTGCGCT CTGCTGAAGC	6500
CAGTTACCTT CGGAAAAGA GTTGGTAGCT CTTGATCCGG CAAACAAACC	6550

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FIGURE 5F

ACCGCTGGTA	GCGGTGGTTT	TTTTGTTTGC	AAGCAGCAGA	TTACGCGCAG	6600
AAAAAAGGA	TCTCAAGAAG	ATCCTTTGAT	CTTTTCTACG	GGGTCTGACG	6650
CTCAGTGGAA	CGAAAACTCA	CGTTAAGGGA	TTTTGGTCAT	GAGATTATCA	6700
AAAAGGATCT	TCACCTAGAT	CCTTTTAAAT	TA\AAATGAA	GTTTTAAATC	6750
AATCTAAAGT	ATATATGAGT	AACTTGGTC	TGACAGTTAC	CAATGCTTAA	6800
TCAGTGAGGC	ACCTATCTCA	GCGATCTGTC	TATTTTCGTT	ATCCATAGTT	6850
GCCTGACTCC	CCGTCGTGTA	GATAACTACG	ATACGGGAGG	GCTTACCATC	6900
TGGCCCCAGT	GCTGCAATGA	TACCGCGAGA	CCCACGCTCA	CCGGCTCCAG	6950
ATTTATCAGC	AATAAACCAG	CCAGCCGGAA	GGGCCGAGCG	CAGAAGTGGT	7000
CCTGCAACTT	TATCCGCCTC	CATCCAGTCT	ATTAATTGTT	GCCGGGAAGC	7050
TAGAGTAAGT	AGTTCGCCAG	TTAATAGTTT	GCGCAACGTT	GTTGCCATTG	7100
CTGCAGGCAT	CGTGGTGTCA	CGCTCGTCGT	TTGGTATGGC	TTCATTACAGC	7150
TCCGGTTCCC	AACGATCAAG	GCGAGTTACA	TCATCCCCCA	TGTTGTGCAA	7200
AAAAGCGGTT	AGCTCCTTCG	GTCCTCCGAT	CGTTGTCAGA	AGTAAGTTGG	7250
CCGCAGTGTT	ATCACTCATG	GTTATGCCAG	CACTGCATAA	TTCTCTTACT	7300
GTCATGCCAT	CCGTAAGATG	CTTTTCTGTG	ACTGGTGAGT	ACTCAACCAA	7350
GTCATTCTGA	GAATAGTGTA	TGCGGCGACC	GAGTTGCTCT	TGCCCCGGCGT	7400
CAACACGGGA	TAATACCGCG	CCACATAGCA	CAACTTTAAA	AGTGCTCATC	7450
ATTGGA AAAC	GTTCTTCGGG	GCGAAA AACTC	TCAAGGATCT	TACCGCTGTT	7500
GAGATCCAGT	TCGATGTAAC	CCACTCGTGC	ACCCA AACTGA	TCTTCAGCAT	7550
CTTTTACTTT	CACCAGCGTT	TCTGGGTGAG	CAAAAACAGG	AAGGCAAAAT	7600
GCCGCAAAAA	AGGGAATAAG	GGCGACACGG	AAATGTTGAA	TACTCATACT	7650
CTTCCTTTTT	CAATATTATT	GAAGCATTTA	TCAGGGTTAT	TGTCTCATGA	7700
GCGGATACAT	ATTTGAATGT	ATTTAGAAAA	ATAAACAAAT	AGGGGTTCCG	7750
CGCACATTTC	CCCGAAAAGT	GCCACCTGAC	GTCTAAGAAA	CCATTATTAT	7800
CATGACATTA	ACCTATAAAA	ATAGGCGTAT	CACGAGGCCC	TTTCGTCTTC	7850
AA					7852

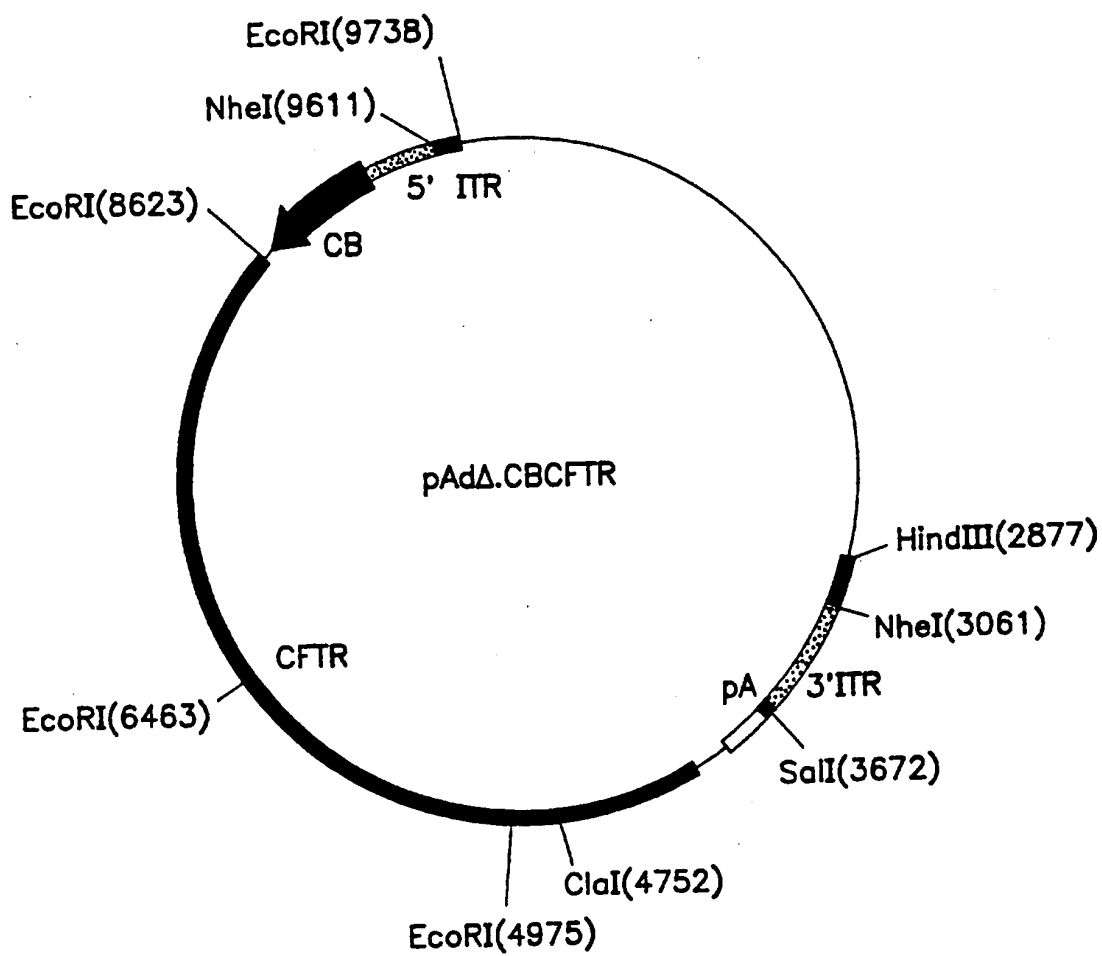


FIG. 6

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FIGURE 7A

TCTCCGCTT	CCTCGCTCAC	TGACTCGCTG	CGCTCGGTCG	TTCGGCTGCG	50
GCGAGCGGTA	TCAGCTCACT	CAAAGGCGGT	AATACGGTTA	TCCACAGAAT	100
CAGGGGATAA	CGCAGGAAAG	AACATGTGAG	CAAAAGGCCA	GCAAAAGGCC	150
AGGAACCGTA	AAAAGGCCGC	GTTGCTGGCG	TTTTTCCATA	GGCTCCGCCC	200
CCCTGACGAG	CATCACAAAA	ATCGACGCTC	AAGTCAGAGG	TGGCGAAACC	250
CGACAGGACT	ATAAAGATAC	CAGGCGTTTC	CCCCTGGAAG	CTCCCTCGTG	300
CGCTCTCCTG	TTCCGACCCT	GCCGCTTACC	GGATACCTGT	CCGCCTTTCT	350
CCCTTCGGGA	AGCGTGCGC	TTTCTCATAG	CTCACGCTGT	AGGTATCTCA	400
GTTCCGGTGTA	GGTCGTTTCG	TCCAAGCTGG	GCTGTGTGCA	CGAACCCCCC	450
GTTCAGCCCG	ACCGCTGCGC	CTTATCCGGT	AACTATCGTC	TTGAGTCCAA	500
CCCGGTAAGA	CACGACTTAT	CGCCACTGGC	AGCAGCCACT	GGTAACAGGA	550
TTAGCAGAGC	GAGGTATGTA	GGCGGTGCTA	CAGAGTTCTT	GAAGTGGTGG	600
CCTAACTACG	GCTACACTAG	AAGAACAGTA	TTTGGTATCT	GCGCTCTGCT	650
GAAGCCAGTT	ACCTTCGGAA	AAAGAGTTGG	TAGCTCTTGA	TCCGGCAAAC	700
AAACCACCGC	TGGTAGCGGT	GGTTTTTTTG	TTTGCAAGCA	GCAGATTACG	750
CGCAGAAAAA	AAGGATCTCA	AGAAGATCCT	TTGATCTTTT	CTACGGGGTC	800
TGACGCTCAG	TGGAACGAAA	ACTCACGTTA	AGGGATTTTG	GTCATGAGAT	850
TATCAAAAAG	GATCTTCACC	TAGATCCTTT	TAAATTAAAA	ATGAAGTTTT	900
AAATCAATCT	AAAGTATATA	TGAGTAAACT	TGGTCTGACA	GTTACCAATG	950
CTTAATCAGT	GAGGCACCTA	TCTCAGCGAT	CTGTCTATTT	CGTTCATCCA	1000
TAGTTGCCTG	ACTCCCCGTC	GTGTAGATAA	CTACGATACG	GGAGGGCTTA	1050
CCATCTGGCC	CCAGTGCTGC	AATGATACCG	CCAGACCCAC	GCTCACCGGC	1100
TCCAGATTTA	TCAGCAATAA	ACCAGCCAGC	CGGAAGGGCC	GAGCGCAGAA	1150
GTGGTCCTGC	AACTTTATCC	GCCTCCATCC	AGTCTATTAA	TTGTTGCCGG	1200
GAAGCTAGAG	TAAGTAGTTC	GCCAGTTAAT	AGTTTGCGCA	ACGTTGTTGC	1250
CATTGCTACA	GGCATCGTGG	TGTCACGCTC	GTCGTTTGGT	ATGGCTTCAT	1300

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FIGURE 7B

TCAGCTCCGC TTCCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG	1350
TGCAAAAAAG CGGTTAGCTC CTTCCGGTCCT CCGATCGTTG TCAGAAGTAA	1400
GTTGGCCGCA GTGTTATCAC TCATGGTTAT GGCAGCACTG CATAATTCTC	1450
TTACTGTCAT GCCATCCGTA AGATGCTTTT CTGTGACTGG TGAGTACTCA	1500
ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT GCTCTTGCCC	1550
GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC	1600
TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG	1650
CTGTTGAGAT CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC	1700
AGCATCTTTT ACTTTCACCA GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC	1750
AAAATGCCGC AAAAAAGGGA ATAAGGGCGA CACGGAAATG TTGAATACTC	1800
ATACTCTTCC TTTTCAATA TTATTGAAGC ATTTATCAGG GTTATTGTCT	1850
CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGG	1900
TTCCGCGCAC ATTTCCCCGA AAAGTGCCAC CTGACGTCTA AGAAACCATT	1950
ATTATCATGA CATTAACCTA TAAAAATAGG CGTATCACGA GGCCCTTTCG	2000
TCTCGCGCGT TTCGGTGATG ACGGTGAAAA CCTCTGACAC ATGCAGCTCC	2050
CGGAGACGGT CACAGCTTGT CTGTAAGCGG ATGCCGGGAG CAGACAAGCC	2100
CGTCAGGGCG CGTCAGCGGG TGTGGCGGG TGTCGGGGCT GGCTTAACTA	2150
TGCGGCATCA GAGCAGATTG TACTGAGAGT GCACCATAAA ATTGTAAACG	2200
TTAATATTTT GTTAAAATTC GCGTTAAATT TTTGTAAAT CAGCTCATTT	2250
TTTAACCAAT AGGCCGAAAT CGGCAAATC CCTTATAAAT CAAAAGAATA	2300
GCCCGAGATA GGGTTGAGTG TTGTTCCAGT TTGGAACAAG AGTCCACTAT	2350
TAAAGAACGT GGA CTCCAAC GTCAAAGGGC GAAAAACCGT CTATCAGGGC	2400
GATGGCCAC TACGTGAACC ATCACCCTAA TCAAGTTTTT TGGGGTCGAG	2450
GTGCCGTAAA GCACTAAATC GGAACCTAA AGGGAGCCCC CGATTTAGAG	2500
CTTGACGGGG AAAGCCGGCG AACGTGGCGA GAAAGGAAGG GAAGAAAGCG	2550
AAAGGAGCGG GCGCTAGGGC GCTGGCAAGT GTAGCGGTCA CGCTGCGCGT	2600

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FIGURE 7C

AACCACCACA	CCCGCCGCGC	TTAATGCGCC	GCTACAGGGC	GCGTACTATG	2650
GTTGCTTTGA	CGTATGCGGT	GTGAAATACC	GCACAGATGC	GTAAGGAGAA	2700
AATACCGCAT	CAGGCGCCAT	TCGCCATTCA	GGCTGCGCAA	CTGTTGGGAA	2750
GGGCGATCGG	TGCGGGCCTC	TTCGCTATTA	CGCCAGCTGG	CGAAAGGGGG	2800
ATGTGCTGCA	AGGCGATTAA	GTTGGGTAAC	GCCAGGGTTT	TCCCAGTCAC	2850
GACGTTGTAA	AACGACGGCC	AGTGCCAAGC	TTAAGGTGCA	CGGCCCACGT	2900
GGCCACTAGT	ACTTCTCGAG	CTCTGTACAT	GTCCGCGGTC	GCGACGTACG	2950
CGTATCGATG	GCGCCAGCTG	CAGGCGGCCG	CCATATGCAT	CCTAGGCCTA	3000
TTAATATTCC	GGAGTATACG	TAGCCGGCTA	ACGTTAACAA	CCGGTACCTC	3050
TAGAACTATA	GCTAGCCAAT	TCCATCATCA	ATAATATACC	TTATTTTGGA	3100
TTGAAGCCAA	TATGATAATG	AGGGGGTGGA	GTTTGTGACG	TGGCGCGGGG	3150
CGTGGAACG	GGGCGGGTGA	CGTAGGTTTT	AGGGCGGAGT	AACTTGATG	3200
TGTTGGGAAT	TGTAGTTTTC	TTAAAATGGG	AAGTTACGTA	ACGTGGGAAA	3250
ACGGAAGTGA	CGATTTGAGG	AAGTTGTGGG	TTTTTTGGCT	TTCGTTTCTC	3300
GGCGTAGGTT	CGCGTGCGGT	TTTCTGGGTG	TTTTTTGTGG	ACTTTAACCG	3350
TTACGTCATT	TTTTAGTCCT	ATATATACTC	GCTCTGCACT	TGGCCCTTTT	3400
TTACACTGTG	ACTGATTGAG	CTGGTGCCGT	GTCGAGTGGT	GTTTTTTTAA	3450
TAGGTTTTCT	TTTTTACTGG	TAAGGCTGAC	TGTTAGGCTG	CCGCTGTGAA	3500
GCGCTGTATG	TTGTTCTGGA	GCGGGAGGGT	GCTATTTTGC	CTAGGCAGGA	3550
GGGTTTTTCA	GGTGTTTATG	TGTTTTTCTC	TCCTATTAAT	TTTGTTATAC	3600
CTCCTATGGG	GGCTGTAATG	TTGTCTCTAC	GCCTGCGGGT	ATGTATTCCC	3650
CCCAAGCTTG	CATGCCTGCA	GGTCGACTCT	AGAGGATCCG	AAAAAACCTC	3700
CCACACCTCC	CCCTGAACCT	GAAACATAAA	ATGAATGCAA	TTGTTGTTGT	3750
TAACTTGTTT	ATTGCAGCTT	ATAATGGTTA	CAAATAAAGC	AATAGCATCA	3800
CAAATTTTCA	AAATAAAGCA	TTTTTTTTCAC	TGCATTCTAG	TTGTGGTTTG	3850
TCCAAACTCA	TCAATGTATC	TTATCATGTC	TGGATCCCCC	TAGCTTGCCA	3900

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FIGURE 7D

AACCTACAGG TGGGGTCTTT CATTCCCCC TTTTCTGGA GACTAAATAA	3950
AATCTTTTAT TTTATCTATG GCTCGTACTC TATAGGCTTC AGCTGGTGAT	4000
ATTGTTGAGT CAAAAC TAGA GCCTGGACCA CTGATATCCT GTCTTTAACA	4050
AATTGGACTA ATCGCGGGAT CAGCCAATTC CATGAGCAA TGTCCCATGT	4100
CAACATTTAT GCTGCTCTCT AAAGCCTTGT ATCTTGCATC TCTTCTTCTG	4150
TCTCCTCTTT CAGAGCAGCA ATCTGGGGCT TAGACTTGCA CTTGCTTGAG	4200
TTCCGGTGGG GAAAGAGCTT CACCCTGTCG GAGGGGCTGA TGGCTTGCCG	4250
GAAGAGGCTC CTCTCGTTCA GCAGTTTCTG GATGGAATCG TACTGCCGCA	4300
CTTTGTTCTC TTCTATGACC AAAAATTGTT GGCATTCCAG CATTGCTTCT	4350
ATCCTGTGTT CACAGAGAAT TACTGTGCAA TCAGCAAATG CTTGTTTTAG	4400
AGTTCTTCTA ATTATTTGGT ATGTTACTGG ATCCAAATGA GCACTGGGTT	4450
CATCAAGCAG CAAGATCTTC GCCTTACTGA GAACAGATCT AGCCAAGCAC	4500
ATCAACTGCT TGTGGCCATG GCTTAGGACA CAGCCCCCAT CCACAAGGAC	4550
AAAGTCAAGC TTCCCAGGAA ACTGTTCTAT CACAGATCTG AGCCCAACCT	4600
CATCTGCAAC TTTCCATATT TCTTGATCAC TCCACTGTTC ATAGGGATCC	4650
AAGTTTTTTC TAAATGTTCC AGAAAAATA AATACTTTCT GTGGTATCAC	4700
TCCAAAGGCT TTCCTCCACT GTTGCAAAGT TATTGAATCC CAAGACACAC	4750
CATCGATCTG GATTTCTCCT TCAGTGTTC A GTAGTCTCAA AAAAGCTGAT	4800
AACAAAGTAC TCTTCCCTGA TCCAGTTCTT CCCAAGAGGC CCACCCTCTG	4850
GCCAGGACTT ATTGAGAAGG AAATGTTCTC TAATATGGCA TTTCCACCTT	4900
CTGTGTATTT TGCTGTGAGA TCTTTGACAG TCATTTGGCC CCCTGAGGGC	4950
CAGATGTCAT CTTTCTTCAC GTGTGAATTC TCAATAATCA TAACTTTCTGA	5000
GAGTTGGCCA TTCTTGATG GTTTGGTTGA CTTGGTAGGT TTACCTTCTG	5050
TTGGCATGTC AATGAACCTA AAGACTCGGC TCACAGATCG CATCAAGCTA	5100
TCCACATCTA TGCTGGAGTT TACAGCCAC TGCAATGTAC TCATGATATT	5150
CATGGCTAAA GTCAGGATAA TACCAACTCT TCCTTCTCCT TCTCCTGTTG	5200

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FIGURE 7E

TTAAAATGGA	AATGAAGGTA	ACAGCAATGA	AGAAGATGAC	AAAAATCATT	5250
TCTATTCTCA	TTTGGAACCA	GCGCAGTGTT	GACAGGTACA	AGAACCAGTT	5300
GGCAGTATGT	AAATTCAGAG	CTTTGTGGAA	CAGAGTTTCA	AAGTAAGGCT	5350
GCCGTCCGAA	GGCACGAAGT	GTCCATAGTC	CTTTTAAGCT	TGTAACAAGA	5400
TGAGTGAAAA	TTGGACTCCT	GCCTTCAGAT	TCCAGTTGTT	TGAGTTGCTG	5450
TGAGGTTTGG	AGGAAATATG	CTCTCAACAT	AATAAAAGCC	ACTATCACTG	5500
GCACTGTTGC	AACAAAGATG	TAGGGTTGTA	AAACTGCGAC	AACTGCTATA	5550
GCTCCAATCA	CAATTAATAA	CAACTGGATG	AAGTCAAATA	TGGTAAGAGG	5600
CAGAAGGTCA	TCCAAAATTG	CTATATCTTT	GGAGAATCTA	TTAAGAATCC	5650
CACCTGCTTT	CAACGTGTTG	AGGGTTGACA	TAGGTGCTTG	AAGAACAGAA	5700
TGTAACATTT	TGTGGTGTA	AATTTTCGAC	ACTGTGATTA	GAGTATGCAC	5750
CAGTGGTAGA	CCTCTGAAGA	ATCCCATAGC	AAGCAAAGTG	TCGGCTACTC	5800
CCACGTAAAT	GTAAACACA	TAATACGAAC	TGGTGCTGGT	GATAATCACT	5850
GCATAGCTGT	TATTTCTACT	ATGAGTACTA	TTCCCTTTGT	CTTGAAGAGG	5900
AGTGTTTCCA	AGGAGCCACA	GCACAACCAA	AGAAGCAGCC	ACCTCTGCCA	5950
GAAAAATTAC	TAAGCACCAA	ATTAGCACAA	AAATTAAGCT	CTTGTGGACA	6000
GTAATATATC	GAAGGTATGT	GTTCCATGTA	GTCAGTGCTG	GTATGCTCTC	6050
CATATCATCA	AAAAAGCACT	CCTTTAAGTC	TTCTTCGTTA	ATTTCTTCAC	6100
TTATTTCCAA	GCCAGTTTCT	TGAGATAACC	TTCTTGAATA	TATATCCAGT	6150
TCAGTCAAGT	TTGCCTGAGG	GGCCAGTGAC	ACTTTTCGTG	TGGATGCTGT	6200
TGTCTTTCGG	TGAATGTTCT	GACCTTGTTT	AACTGAGTGT	GTCATCAGGT	6250
TCAGGACAGA	CTGCCTCCTT	CGTGCCTGAA	GCGTGGGGCC	AGTGCTGATC	6300
ACGCTGATGC	GAGGCAGTAT	CGCCTCTCCC	TGCTCAGAAT	CTGGTACTAA	6350
GGACAGCCTT	CTCTCTAAAG	GCTCATCAGA	ATCCTCTTCG	ATGCCATTCA	6400
TTTGTAAGGG	AGTCTTTTGC	ACAATGGAAA	ATTTTCGTAT	AGAGTTGATT	6450
GGATTGAGAA	TAGAATTCTT	CCTTTTTTCC	CCAAACTCTC	CAGTCTGTTT	6500

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FIGURE 7F

AAAAGATTGT TTTTGTGTTT CTGTCCAGGA GACAGGAGCA TCTCCTTCTA	6550
ATGAGAAACG GTGTAAGGTC TCAGTTAGGA TTGAATTTCT TCTTTCTGCA	6600
CTAAATTGGT CGAAAGAATC ACATCCCATG AGTTTTGAGC TAAAGTCTGG	6650
CTGTAGATTT TGGAGTCTG AAAATGTCCC ATAAAAATAG CTGCTACCTT	6700
CATGCAAAAT TAATATTTTG TCAGCTTTCT TTAAATGTTT CATTTTAGAA	6750
GTGACCAAAA TCCTAGTTTT GTTAGCCATC AGTTTACAGA CACAGCTTTC	6800
AAATATTTCT TTTTCTGTGA AAACATCTAG GTATCCAAAA GGAGAGTCTA	6850
ATAAATACAA ATCAGCATCT TTGTATACTG CTCTTGCTAA AGAAATTCTT	6900
GCTCGTTGAC CTCCACTCAG TGTGATTCCA CCTTCTCCAA GAACTATATT	6950
GTCTTTCTCT GCAAACCTGG AGATGTCCTC TTCTAGTTGG CATGCTTTGA	7000
TGACGCTTCT GTATCTATAT TCATCATAGG AAACACCAAA GATGATATTT	7050
TCTTTAATGG TGCCAGGCAT AATCCAGGAA AACTGAGAAC AGAATGAAAT	7100
TCTTCCACTG TGCTTAATTT TACCCTCTGA AGGCTCCAGT TCTCCCATAA	7150
TCATCATTAG AAGTGAAGTC TTGCCTGCTC CAGTGGATCC AGCAACCGCC	7200
AACAACGTGC CTCTTTCTAT CTTGAAATTA ATATCTTTCA GGACAGGAGT	7250
ACCAAGAAGT GAGAAATTAC TGAAGAAGAG GCTGTCATCA CCATTAGAAG	7300
TTTTTCTATT GTTATTGTTT TGTTTTGCTT TCTCAAATAA TTCCCCAAT	7350
CCCTCCTCCC AGAAGGCTGT TACATTCTCC ATCACTACTT CTGTAGTCGT	7400
TAAGTTATAT TCCAATGTCT TATATTCTTG CTTTGTGAAG AAATCCTGTA	7450
TTTTGTTTAT TGCTCCAAGA GAGTCATACC ATGTTTGTAC AGCCCAGGGA	7500
AATTGCCGAG TGACCGCCAT GCGCAGAACA ATGCAGAATG AGATGGTGGT	7550
GAATATTTTC CGGAGGATGA TTCCTTTGAT TAGTGATAG GGAAGCACAG	7600
ATAAAACAC CACAAAGAAC CCTGAGAAGA AGAAGGCTGA GCTATTGAAG	7650
TATCTCACAT AGGCTGCCTT CCGAGTCAGT TTCAGTTCTG TTTGTCTTAA	7700
GTTTTCAATC ATTTTTTCCA TTGCTTCTTC CCAGCAGTAT GCCTTAACAG	7750
ATTGGATGTT CTCGATCATT TCTGAGGTAA TCACAAGTCT TTCCTGATC	7800

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FIGURE 7G

TTCCCAGCTC	TCTGATCTCT	GTACTTCATC	ATCATTCTCC	CTAGCCCAGC	7850
CTGAAAAAGG	GCAAGGACTA	TCAGGAAACC	AAGTCCACAG	AAGGCAGACG	7900
CCTGTAACAA	CTCCCAGATT	AGCCCCATGA	GGAGTGCCAC	TTGCAAAGGA	7950
GCGATCCACA	CGAAATGTGC	CAATGCAAGT	CCTTCATCAA	ATTTGTTTCTAG	8000
GTTGTTGGAA	AGGAGACTAA	CAAGTTGTCC	AATACTTATT	TTATCTAGAA	8050
CACGGCTTGA	CAGCTTTAAA	GTCTTCTTAT	AAATCAAAC	AAACATAGCT	8100
ATTCTCATCT	GCATTCCAAT	GTGATGAAGG	CCAAAAATGG	CTGGGTGTAG	8150
GAGCAGTGTC	CTCACAATAA	AGAGAAGGCA	TAAGCCTATG	CCTAGATAAA	8200
TCGCGATAGA	GCGTTCCTCC	TTGTTATCCG	GGTCATAGGA	AGCTATGATT	8250
CTTCCCAGTA	AGAGAGGCTG	TACTGCTTTG	GTGACTTCCC	CTAAATATAA	8300
AAAGATTCCA	TAGAACATAA	ATCTCCAGAA	AAAACATCGC	CGAAGGGCAT	8350
TAATGAGTTT	AGGATTTTTC	TTTGAAGCCA	GCTCTCTATC	CCATTCTCTT	8400
TCCAATTTTT	CAGATAGATT	GTCAGCAGAA	TCAACAGAAG	GGATTTGGTA	8450
TATGTCTGAC	AATTCAGGC	GCTGTCTGTA	TCCTTTCCTC	AAAATTGGTC	8500
TGGTCCAGCT	GAAAAAAGT	TTGGAGACAA	CGCTGGCCTT	TTCCAGAGGC	8550
GACCTCTGCA	TGGTCTCTCG	GGCGCTGGGG	TCCCTGCTAG	GGCCGTCTGG	8600
GCTCAAGCTC	CTAATGCCAA	AGGAATTCTT	GCAGCCCGGG	GGATCCACTA	8650
GTTCTAGAGC	GGCCGCCACC	GCGGTGGCTG	ATCCCGCTCC	CGCCCGCCGC	8700
GCGCTTCGCT	TTTTATAGGG	CCGCCGCCGC	CGCCGCCTCG	CCATAAAAGG	8750
AAACTTTCGG	AGCGCGCCGC	TCTGATTGGC	TGCCGCCGCA	CCTCTCCGCC	8800
TCGCCCCGCC	CCGCCCCCTCG	CCCCGCCCCG	CCCCGCCTGG	CGCGCGCCCC	8850
CCCCCCCCC	CCGCCCCCAT	CGCTGCACAA	AATAATTAAA	AAATAAATAA	8900
ATACAAAATT	GGGGGTGGGG	AGGGGGGGGA	GATGGGGAGA	GTGAAGCAGA	8950
ACGTGGCCTC	GAGTAGATGT	ACTGCCAAGT	AGGAAAGTCC	CATAAGGTCA	9000
TGTACTGGGC	ATAATGCCAG	GCGGGCCATT	TACCGTCATT	GACGTCAATA	9050
GGGGGCGTAC	TTGGCATATG	ATACACTTGA	TGTACTGCCA	AGTGGGCAGT	9100

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FIGURE 7H

TTACCGTAAA TACTCCACCC ATTGACGTCA ATGGAAAGTC CCTATTGGCG	9150
TTACTATGGG AACATACGTC ATTATTGACG TCAATGGGCG GGGGTCGTTG	9200
GGCGGTCAGC CAGGCGGGCC ATTTACCGTA AGTTATGTAA CGACCTGCAG	9250
GCTGATCTCC CTAGACAAAT ATTACGCGCT ATGAGTAACA CAAAATTATT	9300
CAGATTTTAC TTCCTCTTAT TCAGTTTTCC CGCGAAAATG GCCAAATCTT	9350
ACTCGGTTAC GCCCAAATTT ACTACAACAT CCGCCTAAAA CCGCGCGAAA	9400
ATTGTCACTT CCTGTGTACA CCGGCGCACA CCAAAAACGT CACTTTTGCC	9450
ACATCCGTCG CTTACATGTG TTCCGCCACA CTTGCAACAT CACACTTCCG	9500
CCACACTACT ACGTCACCCG CCCC GTTCCC ACGCCCCGCG CCACGTCACA	9550
AACTCCACCC CCTCATTATC ATATTGGCTT CAATCCAAAA TAAGGTATAT	9600
TATTGATGAT GCTAGCATGC GCAAATTTAA AGCGCTGATA TCGATCGCGC	9650
GCAGATCTGT CATGATGATC ATTGCAATTG GATCCATATA TAGGGCCCCG	9700
GTTATAATTA CCTCAGGTCG ACGTCCCATG GCCATTGCGAA TTCGTAATCA	9750
TGGTCATAGC TGTTTCCTGT GTGAAATTGT TATCCGCTCA CAATTCCACA	9800
CAACATACGA GCCGGAAGCA TAAAGTGTA AGCCTGGGGT GCCTAATGAG	9850
TGAGCTAACT CACATTAATT GCGTTGCGCT CACTGCCCCG TTTCCAGTCG	9900
GGAAACCTGT CGTGCCAGCT GCATTAATGA ATCGGCCAAC GCGCGGGGAG	9950
AGGCGGTTTG CGTATTGGGC GC	9972

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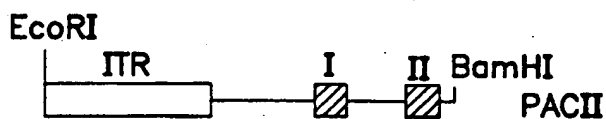


FIG. 8A

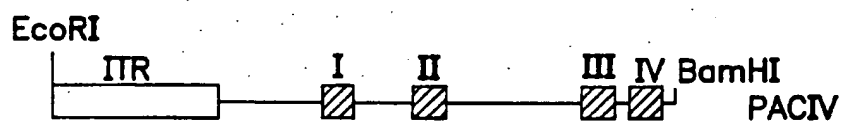


FIG. 8B

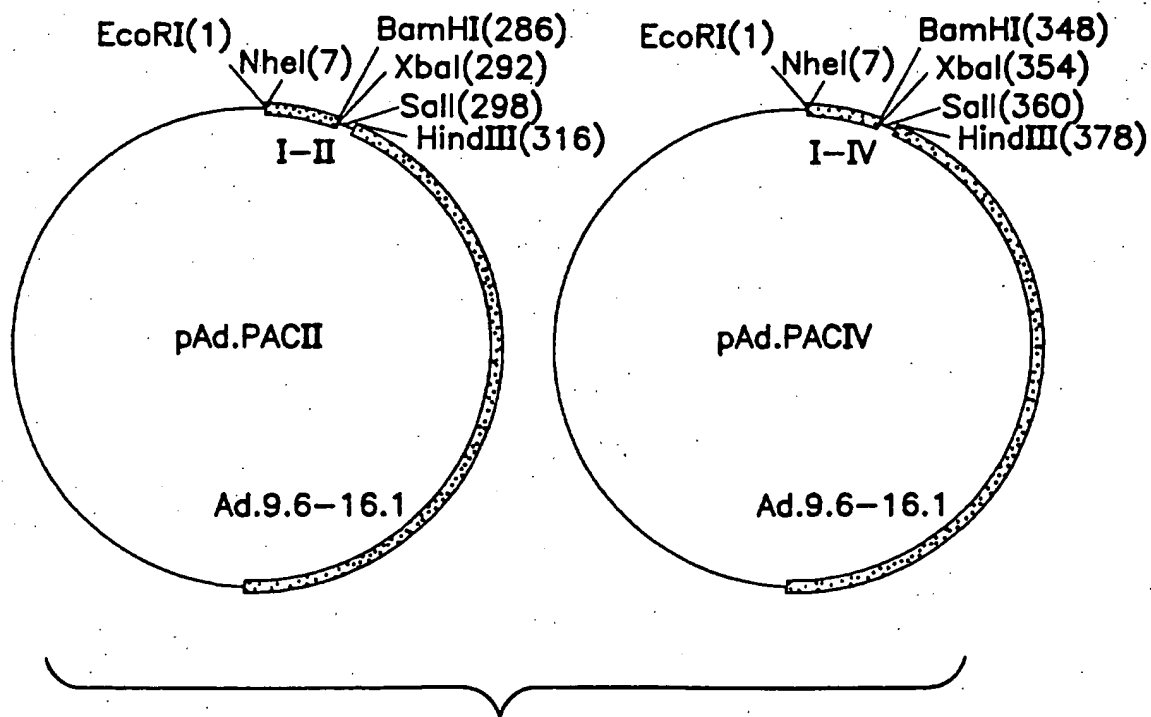
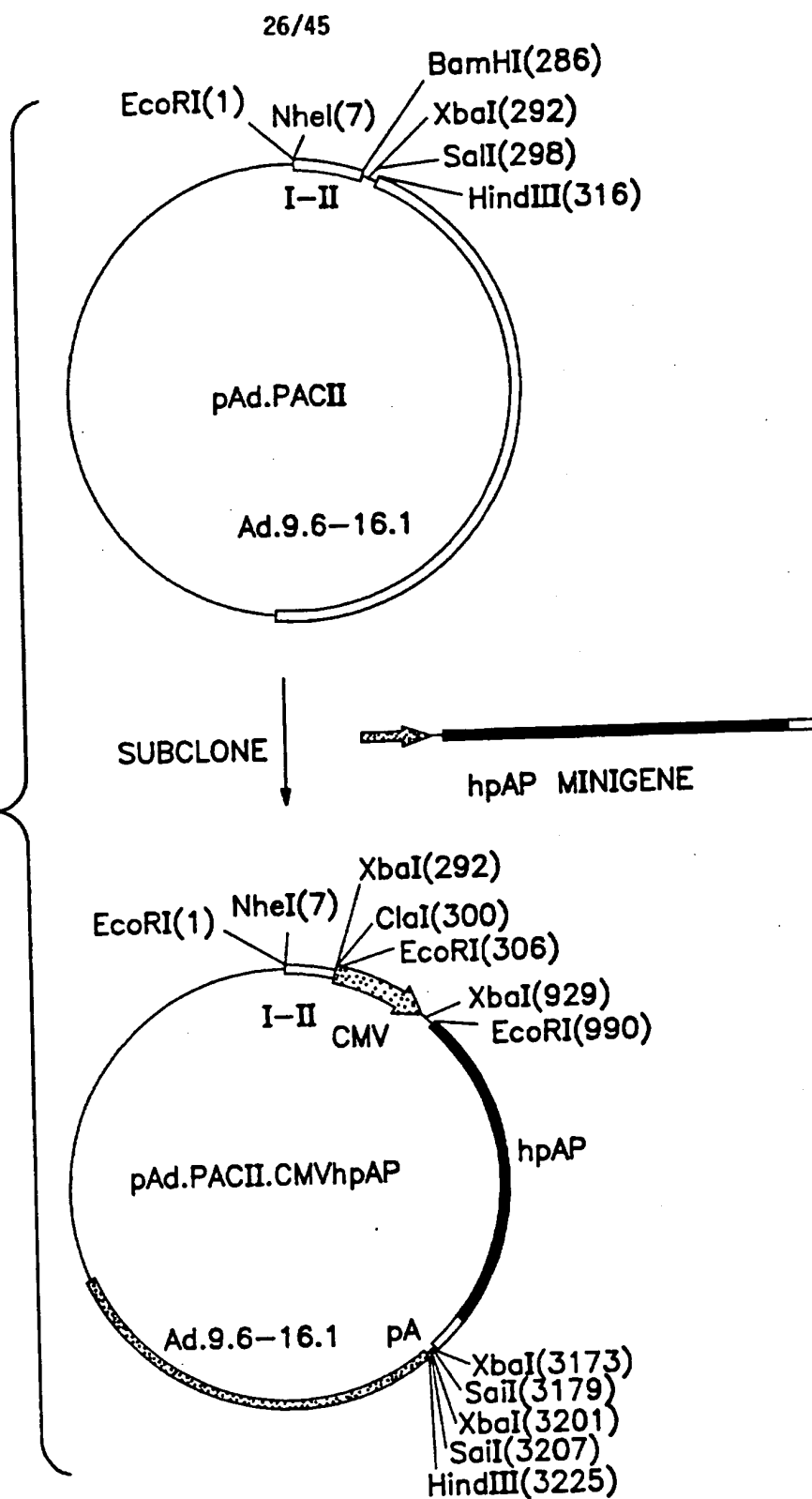


FIG. 8C

FIG. 9A



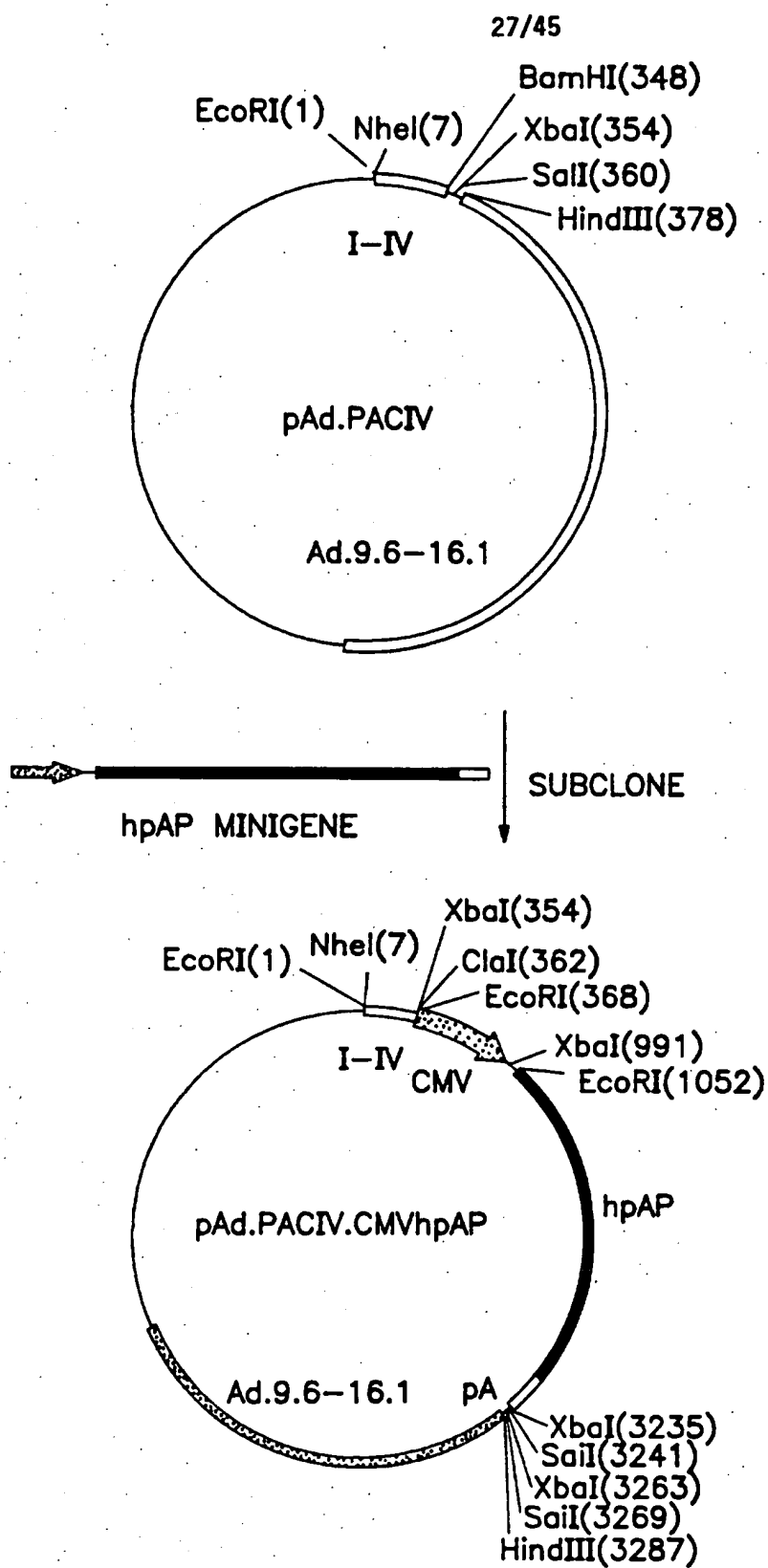
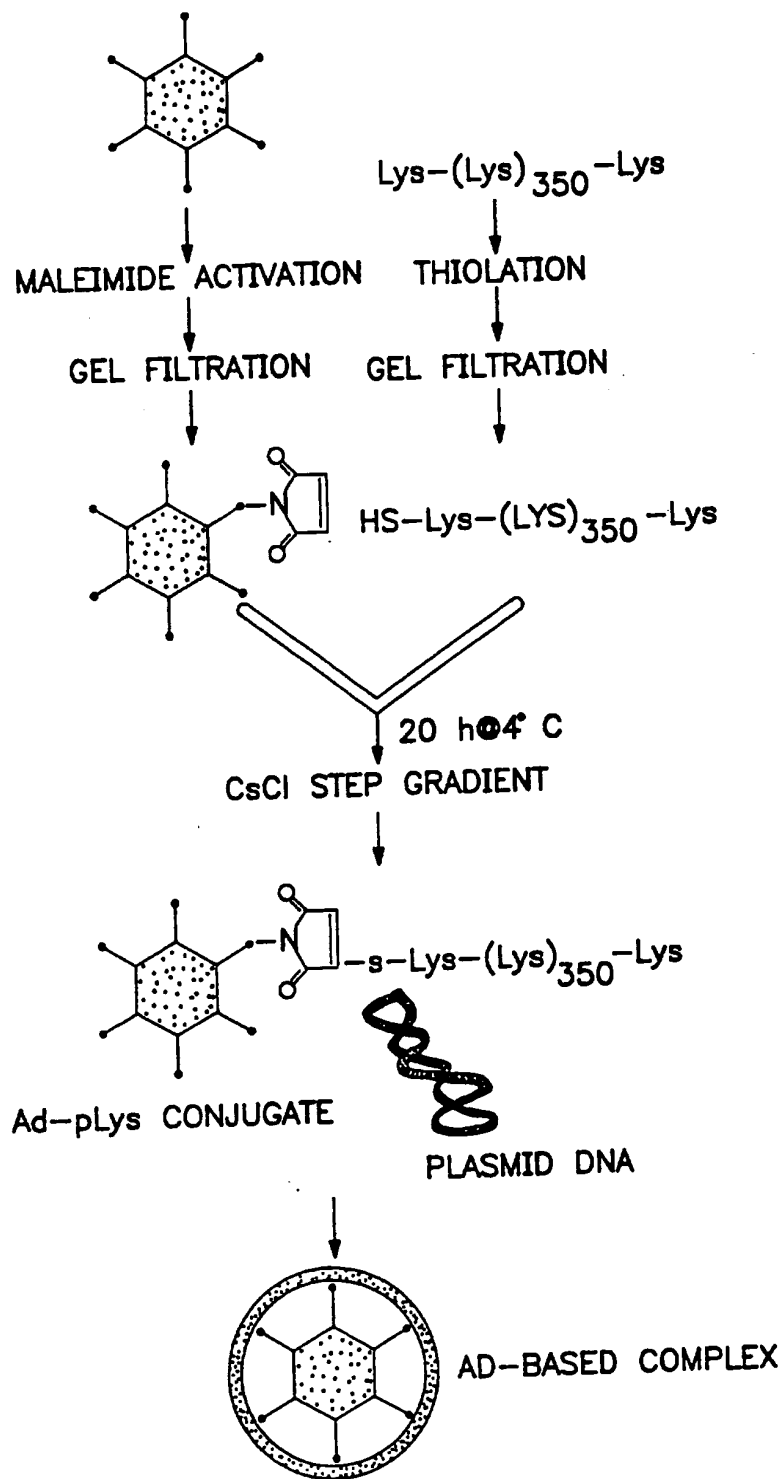


FIG. 9B

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FIG. 10



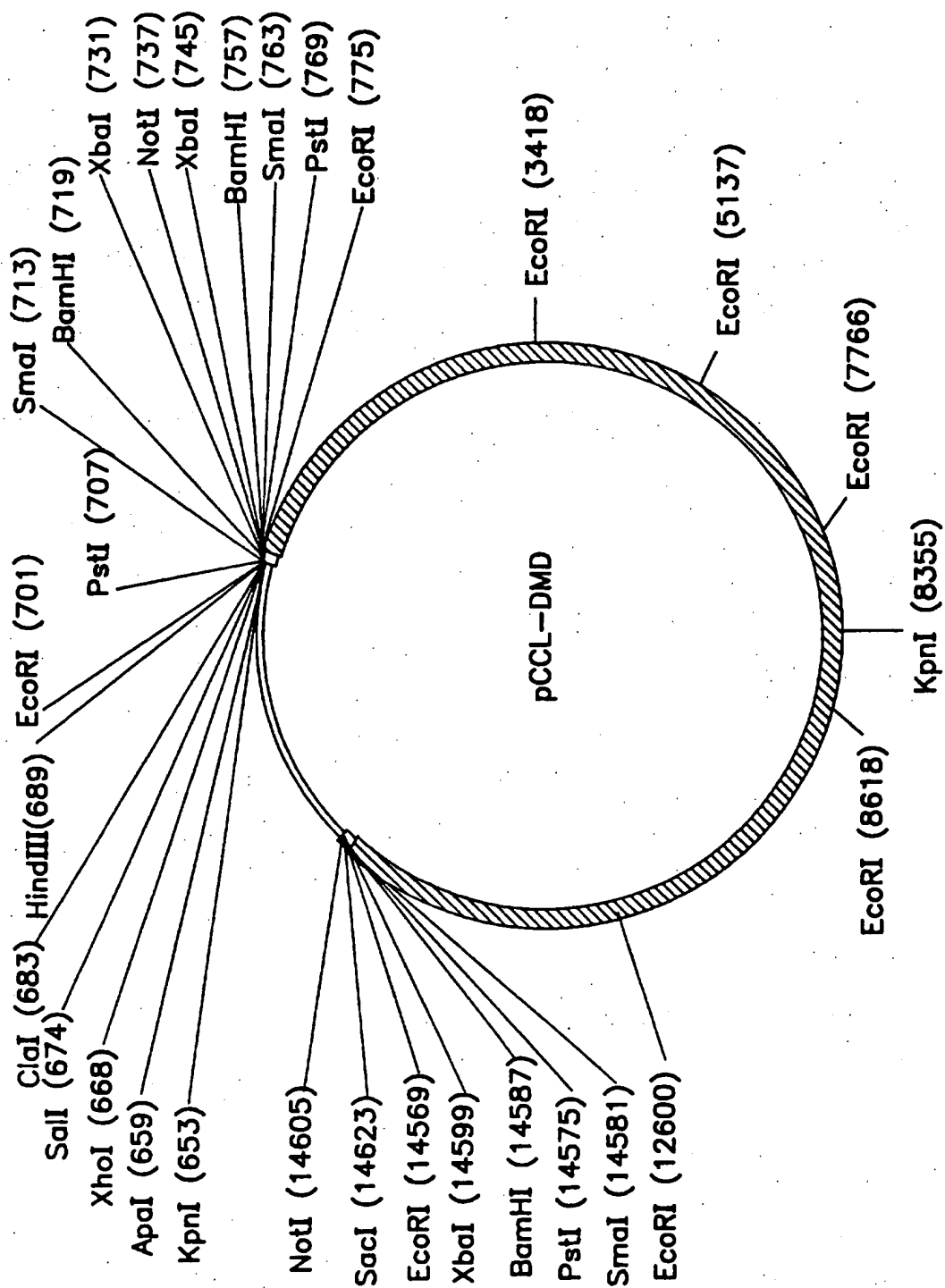


FIG. 11

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FIGURE 12A

CCAATTCCAT CATCAATAAT ATACCTTATT TTGGATTGAA GCCAATATGA	50
TAATGAGGGG GTGGAGTTTG TGACGTGGCG CGGGGCGTGG GAACGGGGCG	100
GGTGACGTAG GTTTTAGGGC GGAGTAACTT GTATGTGTTG GGAATTGTAG	150
TTTTCTTAAA ATGGGAAGTT ACGTAACGTG GGAAAACGGA AGTGACGATT	200
TGAGGAAGTT GTGGGTTTTT TGGCTTTCGT TTCTGGGCGT AGGTTTCGCGT	250
GCGGTTTTCT GGGTGTTTTT TGTGGACTTT AACCGTTACG TCATTTTTTA	300
GTCCTATATA TACTCGCTCT GCACTTGGCC CTTTTTTACA CTGTGACTGA	350
TTGAGCTGGT GCCGTGTCGA GTGGTGTTTT TTTAATAGGT TTTCTTTTTT	400
ACTGGTAAGG CTGACTGTTA GGCTGCCGCT GTGAAGCGCT GTATGTTGTT	450
CTGGAGCGGG AGGGTGCTAT TTTGCCTAGG CAGGAGGGTT TTTCAGGTGT	500
TTATGTGTTT TTCTCTCCTA TTAATTTTGT TATACCTCCT ATGGGGGCTG	550
TAATGTTGTC TCTACGCCTG CGGGTATGTA TTCCCCCAA GCTTGCATGC	600
CTGCAGGTCG ACTCTAGAGG ATCCGAAAAA ACCTCCCACA CCTCCCCCTG	650
AACCTGAAAC ATAAAATGAA TGCAATTGTT GTTGTTAACT TGTTTATTGC	700
AGCTTATAAT GGTACAAAT AAAGCAATAG CATCACAAAT TTCACAAATA	750
AAGCATTTTT TTCACTGCAT TCTAGTTGTG GTTTGTCCAA ACTCATCAAT	800
GTATCTTATC ATGTCTGGAT CCCC GCGGCC GCTCTAGAAC TAGTGGATCC	850
CCCCGGCTGC AGGAATTCCG TAACATAACT GCGTGCTTTA TTGAGATACA	900
CAGTAAAGCA GTAATATAAT ACAATAGTAA GGCATATATT TGGTGAAATC	950
TGATATGTTG TGAAAATGCA GTAAACTGA AGTTTAAAAA AATAATTAGT	1000
AAATGTTACA GTGTTGGTGT TAAACACAA TCTATTATGA TACTCAAGTA	1050
AGAGTCCAGT ACCTGGAGAC AATGATGATA CATGCCATGT GATGATTATG	1100
CTTCAGTTAC ACTGATTATG ATTTACACTT TAATACTTGA TGGTTATAAA	1150
GAACATGAAA TGATGTCCAA ATTATGCTTA AAATCAGCAA TAAAGCTCTC	1200
AGTTTTTATT CAAATATTTT GATAGATTCA CTCCAGAACT AATATCTAAA	1250

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FIGURE 12B

AGATAAAACG	AAAAGATTAA	AACAAAAC	TGCACTCTAT	CTACCTTGGA	1300
TTTTAGAATG	AAACTTAAAA	CTTCTTAGTA	GGAAAGGAAC	CCCTTGTTTT	1350
AAATCTTGGT	GAAAACAAAT	CCTTGGATAA	AGAAAATGCC	CAGTGCCACA	1400
TAAAGGAGAG	AGAGAGAGAA	AAGCAAGACC	AGAACCAAAT	TTCAATTTGT	1450
TATCTTAGAG	CTTTGGGTTT	TCTTTTGGAA	ATTATAAATG	AAAAAAGGAA	1500
ACTGGTGTCC	ACACAACAGA	CAAGTGGTGA	AGTTGTGAAA	TTAGGTGTGC	1550
ACAATTACTA	GAAACACCCC	AAAACCAAAG	TGAGGTAGAA	ATAGCATGAG	1600
AAGCTGTGTT	TGATGTTAAT	TACAATTAAT	AATGGACAAA	ACCCACTCGC	1650
TAGAAGTTAA	TTACACTTGA	CGTTAGAGGT	AACAGATTTG	CAAATGATA	1700
GGACAGTGAT	TTCTATTGAG	AGAATGCTCT	TTAAATGCTA	AGAAGAAGAA	1750
ACTGGCATGA	GAGGAGTAAA	GCTCTTCCTA	GCAGTCCTTA	GCTTTCTGTT	1800
GCACTTTTTT	TCCTGGTTCA	ATGACTTGCA	TTTGTTTAGA	CATTTCAGCC	1850
CGTCAACTAG	ACCAGAGAGT	TTGGAGACGC	TTTTGCTCTC	AAAACTTTCC	1900
AACCACTGTG	CCTTCTCACC	CACAATCCTG	TGTGGAGTTA	CTTGCAGGGA	1950
AACCAATGCA	AAGGAGACAA	ATGCAGTTCA	TGGGCTTCTG	GA CTGATATT	2000
CACCAGGGTC	ACAATGTGAT	TGGGTTACTT	TCTTAACAGT	AATCCTAAGT	2050
CTTGCAGCAT	TAAAAA	AATCATCACA	ATGAAGAAAA	AAAAACCCAA	2100
AAAATCTAAA	ATCTAAAATT	CATCATCATC	ATCAACAACA	ACAACAACAA	2150
CAACAACAAA	ACCACCCACT	TCAGGTTGAG	TTTATGAAGA	GGGCAGAACA	2200
ATTTAGTTGT	AATTATAGAG	ATGTTTATAT	GTATAGTTGT	AAATATTCAT	2250
CCATTCTTTT	ACAGAGTTGT	TGCTCCCCTC	ATATAAATTG	ACTGAGGAGC	2300
CGCAACCTTT	AGCTCCTACC	ATCTTCCTCC	TACTGTCTGG	GAGTTAAAAA	2350
TGTCATCTGA	TGTTCTATTG	CAGAAACATC	ATTAAATATA	ACCCAACAGT	2400
AGGAAGTTGA	ATATATCAGC	CAACAAATTA	CTATGATAGT	AAGTCCTGTG	2450
TATTCATTCTG	CATGTTCTT	GAAAAAATG	AATCCTCTAG	CTCTCAGTGG	2500

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FIGURE 12C

AAAGTTTAAA ACTAGAAACA TCTGGAGCCC TAGACAATAT TTTAGTGTGG	2550
CGGTAGTCTC CTGGCTTTGG GCTCCAGGGA AAATTCACCTC TTGCCCAAGC	2600
AGATAAGCCC AGATGACTAG AAGCAATTTT CA ^{TT} TAGGAAG TGGCAAGAAC	2650
ATTTGAAGAA GTAACCTTCAT ATCTATTTAT CTATATACCT ATAGTATTTA	2700
TATACTTGTA GACATATAGA TGTATAAAAT GAAAGCCCCAT AGCCAGCCCC	2750
ACTCAGTCAA CAATTCTCAA AAGAGCAATA TGAAGCAGTC ATTTGGTGGG	2800
GTTTCGTATGC AAGAAAATAA AAAAACGTCA TGAATTCCAT ATGAATACCA	2850
CGCTAAAGTA ATGCAAAACA ATGTGCTGCC TCAGTGTGTG TGTGTGTGTG	2900
TGTGTGTGTG GTGGGTTCGT GCATGTATGT GTGCGTGTGT GTGTGTGTGT	2950
GTGTGTGTGT GTGTGTGTGC GTGTGTGTTT GTTTAGGGGT TTTTATAAAC	3000
AACTTTTTTT ATAAAGCACA CTTTAGTTTA CAATCTCTCT TTATAACTGT	3050
TATAAATTTT TAAACAACCC AAAATGCGTT CCATATAAAG AAATGGCAAG	3100
TTATTTAGCT ATCAAGATTT TACATGTTTT CTTTAACTT TTTTGTACAA	3150
TTGCATAGAC GTGTAAAACC TGCCATTGTT AACAAAACAA TAACAGACTT	3200
AGAAACTACT GAAATCTACA GTATAGTACC ACTACCCTTC AAAAAATAT	3250
AGATTTTATT TCTTGTAAC TCTTACTGTC TAATCCTCTT TGTGTACGA	3300
ATATTATAAA AACCATGCGG GAATCAGGAG TTGTAAAACA TTTATTCTGC	3350
TCCTTCTTCA TCTGTCATGA CTGAAACTAA GGA ^{CT} CCATC GCTCTGCCCA	3400
AATCATCTGC CATGTGGAAA AGGCTTCCTA CATGTGTGCC TCTCTCATTG	3450
GCTTTCGGG GGCATTCTT CCTCTGAAC TAGGGAAGGA GTTGTGAGT	3500
TGCTCCATCA CTTCTTCTAA CCCTGTGCTT GTGTCCTGGG GAGGACTCAG	3550
AAGATCTTCC TCACCCATAG ATTCTGAAGT TTGACTGCCA ACCACTCGGA	3600
GCAGCATAGG CTGACTGCTA TCTGACCTCT GCAGAGAGGT GGAAGGAGAG	3650
GACACCGTGG TGCCATTCAC CTTAGCTTCA GCCTGGGGCT GCTCCAGGAG	3700
CTGTCTCAGT CTATGTAACT GAGACTCCAG CTGTTTATTG TGSTCTTCCA	3750

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FIGURE 12D

GGATTTGCAT	CCTGGCTTCC	AGGCGTCCTT	TGTGTTGGCG	CAGTAGCTTA	3800
GCCTCAGCAA	TGAGCTCAGC	ATCCCTGGGA	CTCTGAGGAG	AGGTGGGCAT	3850
CATCTCAGGA	GGAGATGGCA	GTGGAGACAG	GCCTTTATGC	TCATGCTGCT	3900
GCTTCAGGCG	ATCATATTCT	GCTTGCAGAT	TCCTGTTTTT	TTCCTCAAGA	3950
TCTGCTAGGA	TTCTCTCTAG	CTCCCCTCTT	TCCTCACTCT	CTAAGGAAAT	4000
CAAGATCTGG	GCAGGACTAC	GAGGCTGGCT	CAGGGGGGAG	TCCTGGTTCA	4050
AACTTTGGCA	GTAATGCTGG	ATTAACAAAT	GTTTCATCATC	TATGCTCTCA	4100
TTAGGAGAGA	TGCTATCATT	TAGATAAGAT	CCATTGCTGT	TTTCCATTTC	4150
TGCTAGCCTG	CTAGCATAAT	GTTCAATGCG	TGAATGAGTA	TCATCGTGTG	4200
AAAGCTGGGG	GGACGAGGCA	GGCGCAGAAT	CTACTGGCCA	GAAGTTGATC	4250
AGAGTAACGG	GAGTTTCCAT	GTTGTCCCCC	TCTAACACAG	TCTGCACTGG	4300
CAGGTAGCCC	ATTGCGGGAT	GCTTCGCAAA	ATACCTTTTG	GTTGCAAATT	4350
TGTTTTTTTAG	TACCTTGCGC	AAGTCGCGAA	CATCTTCTCC	GGATGTAGTC	4400
GGAGTGCAAT	ACTCTACCAT	GGGGTAGTGC	ATTTTATGGC	CCTTTGCAAC	4450
TCGGCCAGAA	AAAAGCAAC	TTTGGCAGAT	GTCATAATTA	AAATGCTTTA	4500
GGCTTCTGTA	CCTGAATCCA	ATGATTGGAC	ACTCCTTACA	GATGTTACAC	4550
TTGGCTTGAT	GCTTGGCAGT	TTCAGCAGCA	GCCACTCTGT	GCAAGACGGG	4600
CAGCCACACC	ATAGACTGGG	GTTCCAGGCG	CATCCAGTCA	AGGAAGAGAG	4650
CAGCTTCAAT	CTCAGGTTTA	TTATTGGCAA	ATTGGAAGCA	GCTCCTGACA	4700
CTCGGCTCAA	TGTTACTGCC	CCCAAAGGAA	GCAACTTCAC	CCAAGTGTCT	4750
TGGGATTTGA	ATAGAATCAT	GCAGAAGAAG	ACCCAGCCTA	CGCTGGTCAC	4800
AAAAGCCAGT	TGAAGTTGCC	ACTTGCTTGA	AAAGGTATCT	GTAAGTGTCT	4850
TCCAAGTGTG	CTTTACACAG	AGAAATGATG	CCAGTTTTAA	AAGACAGGAC	4900
ACGGATCCTC	CCTGTTGCTC	CCGTATCATA	AACATTGAGA	AGCCAGTTGA	4950
GACACATATC	CACACAGAGA	GGGACATTGA	CCAGATTGTT	GTGCTCTTGC	5000
TCCAGACGAT	CATAAATTGT	AGTCAAACAG	TTAATTATCT	GCAGGATATC	5050

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FIGURE 12E

CATGGGCTGG TCATTTTGCT TGAGGTTGTG CTGGTCCAGG GCATCACATG	5100
CAGCTGACAG GCTCAAGAGA TCCAAGCAAA GGGCCTTCTG GAGCCTTCTG	5150
AGCTTCATGG CAGTCCTATA CGCGGAGAAC CTGACATTAT TCAGGTCAGC	5200
TAAAGACTGG TAGAGCTCTG TCATTTTGGG GTGGTCCCAA CAAGTGGTTT	5250
GGGTCTCGTG GTTGATATAG TAGGGCACTT TGTGTTGGTGA GATGGCTCTC	5300
TCCCAGGGAC CCTGAACTGA AGTGGAAGG AAGTGCTGGG ATGCAGGACC	5350
AAAGTCCCTG TGGGCTTCAT GCAGCTGTCT GACACGGTCC TCCACAGCCA	5400
CCTGTAGAAG CCTCCATCTG GTATTCAGAT CTTCCAAAGT GCTGAGGTTA	5450
TAAGGTGAGA GCTGAATGCC CAGTGTGGTC AGCTGATGTG CAAGGTCATT	5500
GACACGATTG ACATTCTCTT TAAGAGGTGC AATTTCTCCC CGAAGTGCCT	5550
TGACTTTTTTC AAGGTGATCT TGCAGAGAGT CAATGAGGAG ATCCCCCACT	5600
GGCTGCCAGG ATCCCTTGAT CACCTCAGCT TGGCGCAACT TGAGGTCCAG	5650
TTCATCGGCA GCTTCCTGAA GTTCCTGGAG TCTTTCAAGA GCTTCATCTA	5700
TTTTTCTCTG CCAATCAGCT GAGCGCAGGT TCAATTTGTC CCATTCAGCG	5750
TTGACCTCTT CAGCCTGCTT TCGTAGGAGC CGAGTGACAT TCTGAGCTCT	5800
TTCTTCAGGA GGCAGTTCTC TGGGCTCCTG GTAGAGTTTC TCTAGTCCTT	5850
CCAAAGGCTG CTCTGTCAGA AATATTCTCA CAGTCTCCAG AGTACTCATG	5900
ATTACAGGTT CTTTAGTTTT CAATTCCCTC TTGAAGGCCC TATGTATATC	5950
ATTCTGCTTC TGAAGTCTG GGAAATCACC ACCGATGGGT GCCTGACGGC	6000
TCAGTTCATC ATCTTTCAGC TGTAGCCAAA CAAGAAGTTC CTGAAGAGAA	6050
AGATGCAAAC GCTTCCACTG GTCAGAACTT GCTTCCAAAT GGGACCTAAT	6100
GTTGAGAGAC TTTTTCTGAA GTTCACTCCA CTTGAAATTC ATGTTATCCA	6150
AACGTCTTTG TAACAGGGGT GCTTCATCCG AACCTTCCAG GGATCTCAGG	6200
ATTTTTTGGC CATTTTCATC AAGATTGTGA TAGATATCTG TGTGAGTTTC	6250
AATTTCTCCT TGGAGATCTT GCCATGGTTT CATCAGCTCT CTGACTCCCC	6300
TGGAGTCTTC TAGGAGCTTC TCCTTACGGG AAGCGTCCTG TAGGACATTG	6350

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FIGURE 12F

GCAGTTGTTT	CTGCTTCCGT	AATCCAGGAA	AGAAACTTCT	CCAGGTCCAG	6400
AGGGAAGTGC	TGCAGTAATC	TATGAGTTTC	TTCCAAAGCA	GCCTCTTGCT	6450
CACTTACTCT	TTTATGAATG	TTTCCCCAAG	AAGTATTGAT	ATTCTCTGTT	6500
ATCATGTGTA	CTTTTCTGGT	ATCATCAGCA	GAATAGTCCC	GAAGAAGTTT	6550
CAGTGCCAAA	TCATTTGCCA	CGTCTACACT	TATCTGCCGT	TGACGGAGGT	6600
CTTTGGCCAA	CTGCTTGGTT	TCTGTGATCT	TCTTTTGGAT	TGCATCTACT	6650
GTGTGAGGAC	CTTCTTTCCA	TGAGTCAAGC	TTGCCTCTGA	CCTGTCCTAT	6700
GACCTGTTTCG	GCTTCTTCCT	TAGCTTCCAG	CCATTGTGTT	GAATCCTTTA	6750
ACATTTCAATT	CAACTGTTGT	CTCCTGTTCT	GCAGCTGTTT	TTGAACCTCA	6800
TCCCAGTGAA	TCTGAATTCT	TTCAATTCTGA	TCAGTAATGA	TTGTTCTAGC	6850
TTCTTGATTG	CTGGTTTTGT	TTTTCAAATT	CTGGGCAGCA	GTAATGAGTT	6900
CTTCCAATTG	GGGGCGTCTC	TGTTCCAAAT	CTTGCAGTGT	TGCCTTCTGT	6950
TTGATGATCA	TTTCATTGAT	GTCTTCCAGA	TCACCCACCA	TCACTCTCTG	7000
TGATTTTATA	ACTCGATCAA	GCAGAGACAG	CCAGTCTGTA	AGTTCTGTCC	7050
AAGCTCGGTT	GAAGTCTGCC	AGTGCAGGTA	CCTCCAACAG	CAAAGAAGAT	7100
GGCATTCTTA	GTTTGGAGAT	GACAGTTTCC	TTAGTAACCA	CAGATTGTGT	7150
CACTAGAGTA	ACAGTCTGAC	TGGCAGAGGC	TCCAGTAGTG	CTCAGTCCAG	7200
GGGCACGGTC	AGGCTGCTTT	GTCCTCAGCT	CCCGAAGTAA	ATGGTTTACA	7250
GCCTCCCACT	CAGACCTCAG	ATCTTCTAAC	TTCTCTTCA	CTGGCTGAGT	7300
GCTTGGTTTT	TCCTTATACA	AATGCTGCCC	TTTCGACAAA	AGCCTTTCCA	7350
CATCCGCTTG	TTTACCGTGA	ACTGTTACTT	CAATCTCCTT	TATGTCAAAC	7400
GGTCCTGCCT	GACTTGCTTG	GTTATAAATT	TCCAAGTGGT	TTCTAATAGG	7450
AGAGACCCAC	AGAAGCAGGT	GATCCAGCTG	CTCTTCAAGC	TGCCTAAAAT	7500
CTTTTAAGTG	AACCTCAAGC	TCTCCTTGTT	TCTCAGGTAA	AGCTCTGGAG	7550
ACCTTTATCC	ACTGGAGATT	TGTCTGTTTG	AGCTTCTTTT	CAAGTTTATC	7600

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FIGURE 12G

TTGCTCTTCT GGCCTTATGG GAGCACTTAC AAGTACTGCT CCTCCTGTTT	7650
CATTTAATTG TTTTAGAATT CCCTGGCGCA GGGGCAACTC TTCTGCCAGT	7700
AACTTGACTT GTTCAAGTTG TTCTTTTAGC TGCTGCTCAT CTCCAAGTGG	7750
AGTAATAGCA ATGTTATCTG CTTCTTCCAG CCACAAAACA AATTCATTTA	7800
AATCTCTTTG AAATTCTGAC AAGACATTCT TTTGTTCTTC AATCCTCTTT	7850
CTCCTTTCTG CCAGCTCTTT GCAGATGTCG TGCCACCGCA GACTCAAGCT	7900
TCCTAATTTT TCTTGTAGAA TATTGACATC TGTTTTTGAA GACTGTTGAA	7950
TTATTTCTTC CCCAGTTGCA TTCAGTGTTT TGACAACAGC TTGACGCTGC	8000
CCAATGCCAT CCTGGAGTTC CTTAAGATAC CATTTGTATT TAGCATGTTT	8050
CCAGTTTTCA GGATTTTGTG TCTTTTGA AAAGTGTTC ACTTCATTCA	8100
GCCATTGATT AAATACCTTC ATATCATAAT GAAAGTGTCG CCATTTTTCA	8150
ACTGATCTGT CGAATCGCCC TTGTCGTTCC TTGTACATTC TATGAAGTTT	8200
TTCCCCCTGG AAATCCATCT GTGCCACGGC TTCCTGTACT TTCACCTTTT	8250
CCATGGAGGT GGCACCTTGC AAGGCTGCTG TCTTCTTCTT GTGAATAATA	8300
TCAATCCGAC CTGAGATTTG TTGCAAATTG TCTTTTATAT TCTTAAGAGA	8350
CTCCTCTTGC TTA AAAAGAT CTTCAAAATC TTTAGCACAG AGTTCAGGAG	8400
TATTTAGAAG ATGATCAACT TCTGAAAGAG CTTGTAAGAT ATGACTGATC	8450
TCGGTCAAAT AAGTAGAAGG CACATAAGAA ACATCCAAAG GCATATCTTC	8500
AGTCGTCACT ACCATAGTTT CTTCATGGAG AGTGTGAATT TGTGCAAAGT	8550
TGAGTCTTCG AAAGTGAGCA AAATTGCTCT CAATTTGCCG CCAGCGCTTG	8600
CTGAGCTGGA TCTGAGTTGG CTCCACTGCC ATTGCGGCCC CATTCTCAGA	8650
CAAGCCCTCA GCTTGCTGC GCACTGCATT CAGCTCCTCT TTCTTCTTCT	8700
GCAATTCACG ATCAATTTCC TTTAATTTTC TTTCATCTCT GGGTTCAGGT	8750
AGGCTGGCTA ATTTTTTTTC AATTTTCATCC AAGCATTTCA GGAGATCATC	8800
AGCCTGCCTC TTGTACTGAT ACCACTGGTG AGAAATTTCT AGGGCCTTTT	8850

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FIGURE 12H

TTCTTCTTTG	AGACCTCAAA	TCCTTGAGAG	CATTATGTTT	TGTCTGTAAC	8900
AGCTGCTGTT	TTATCTTTAT	TTCTCTCGC	TTTCTCTCAT	CTGTGATTCT	8950
TTGTTGTAAG	TTGTCTCCTC	TTTGCAACAA	TTCATTTACA	GTACCCTCAT	9000
TGTCTTCACT	CATATCTTTA	TTGAAGTCTT	CCTCTTTCAG	ATTCACCCCC	9050
TGCTGAATTT	CAGCCTCCAG	TGGTTCAAGC	AATTTTTGTA	TATCTGAGTT	9100
AAACTGCTCC	AATTCCTTCA	AAGGAATGGA	GGCCTTTCCA	GTCTTAATTC	9150
TGTGAGAAAT	AGCTGCAAAT	CGACGGTTGA	GCTCAGAGAT	TTGGGGCTCT	9200
ACTACTTTCC	TGCAGTGGTC	ACCGCGGTTT	GCCATCAATT	TTGCTGCTTG	9250
GTCACGTGTG	GAGTCCACCT	TTGGGCGCAT	GTCATTCATT	TCAGCCTTTA	9300
AACGCTTAAG	AATGTCTTCC	TTTTGTTGTG	GTTTCTTCTT	TTCAGACTCA	9350
TCTAAAAGTT	CATCTGCATG	AATGATCCAC	TTTGTGATTT	GTTCTATGTT	9400
CTGATCAAAG	GTTTCCATGT	GTTTCTGGTA	TTCCAACAAA	AGATTTAGCC	9450
ATTCTTCTAC	TCTGGAGGTG	ACAGCTATCC	AGTTACTGTT	CAGAAGACTC	9500
AGTTTATCTT	CTACCAAGGT	TTCTTTCTTG	CCCAACACCA	TTTTCAAAGA	9550
CTCTCCTAAT	TCTGTAACAC	TCTTCAAGTG	AGCCTTCTGT	TTCTCAATCT	9600
CTTTTTGAGT	AGCCTTTCCC	CAGGCAACTT	CAGAATCCAA	ATTACTTGGC	9650
ATTCCTTCAA	CTGCTGATCT	CTTCGTCAAT	TCTGTATCTG	TTGCTGCCAG	9700
CCATTCTGTT	AAGACATTCA	TTTCCTTTCT	CATCTTACGG	GACAACTTCA	9750
AGCATTTCTC	CAACTGTTGC	TTTCTCTCTG	TTACCTTCGC	ACCCAACTCA	9800
TTGTAATGCA	ATTTCAAAGC	TGTTACTCGT	TCATCAAGCT	CTTTGGGATT	9850
TTCTGTCTGC	TTTTTCTGTA	CAATTTGACG	TCCGGTTTTA	ATCACCATTT	9900
CCACTTCAGA	CTTGACTTCA	CTCAGGCTTT	TATACAAGTT	CACACAATGA	9950
CTTAGTTGTG	ACTGAATTAC	TTCTGTTC	ACACTCTTGG	TTTCCAATGC	10000
AGGCAAATGC	ATCTTGACTT	CATCTAAAAT	CATCTTACTT	TCCTCTAGAC	10050
GTTGTTCAAA	ATTGGCTGGT	TTTTGGAATA	ATCGAAATTT	CATGGAGACA	10100
TCTTGTAATT	TTTTCTGTGC	AACATCAATT	TGTGAAAGAA	CCCTTTGGTT	10150

FIGURE 12I

GGCATCCTTC CCCTGGTTAT GTTTCTTCAT TTCTTCTAAA CTTATCTCAT	10200
GACTTGTCAA ATCTGATTGG ATTTTCTGGG CTTCCTGAGG CATTGAGCT	10250
GCATCCACCT TGTCAGTGAT ATAAGCTGCC AACTGCTTGT CAATGAATTC	10300
AAGCGACTCC TGAATTAAGT GCAAGGACTT TTCAATTTCC TGGGCAGACT	10350
GGATACTCTG TTCAAGCAAC TTTTGTTTCC TCACAGCCTC TTCATGTAGT	10400
TCCCTCCAAC GAGAATTAAA CGTCTCAAGC TCCTCATTGA TCAGTTCATC	10450
CATGACTCCT CCATCTGTAA GAGTCTGTGC CAATAGACGA ATCTGATTTG	10500
GGTTCTCCTC TGAATGATGC ATCAGATTTT CAAGAGATTG TAGCACTTCA	10550
GTGATTTCTT CAGGTCCTGC AGGAACATTT TCCATGGTTT TAAGTTTCAA	10600
TTCTACTTCA TTGAGCCACT TGTTTGCTTT CTCTAAATAT GACAATAACT	10650
CATGCCAACA TGCCCAAAC TCTTCCAAAG TTTTGCATTT TCCATTCAGC	10700
CTGGTGCACA GCCATTGGTA GTTGGTGGTC AGAGTTTCAA GTTCCTTTTT	10750
TAAGGCCTCT TGTGCTGAGG GTGGAGCGTG AGCTATTACA CTATTTACAG	10800
TCTCAGTAAG GAGTTTCACT TTAGTTTCTT TTTGTAGTGC CTCCTCTTTA	10850
GCTCTCTTCA TTTCTTCAAC AGCAGTCTGT AATTCATCTG GAGTTTTATA	10900
TTCAAAATCT CTCTCTAGAT ATTCTTCTTC AGCTTGTCAT ATCCACTCAT	10950
GCATCTCTGA TAGATCTTTT TGGAGGCTTA CGGTTTTATC CAAACCTGCC	11000
TTTAAGGCTT CCTTTCTGGT GTAGACCTGG CGGCATATGT GATCCCACTG	11050
AGTGTTAAGC TCTCTAAGTT CTGTCTCCAG TCTGGATGCA AACTCAAGTT	11100
CAGCTTCACT CTTTATCTTC TGCCACCTT CATTAACACT ATTTAAACTG	11150
GGCTGAATTG TTTGAATATC ACCAACTAAA AGTCTGCATT GTTTGAGCTG	11200
TTTTTTCAGG ATTTCAGCAT CCCCCAGGGC AGGCCATTCC TCTTTCAGGA	11250
AAACATCAAC TTCAGCCATC CATTTCTGTA AGGTTTTTAT GTGATTCTGA	11300
AATTTTCGAA GTTTATTCAT ATGTTCTTCT AGCTTTTGGC AGCTTTCCAC	11350
CAACTGGGAG GAAAGTTTCT TCCAGTGCCC CTCAATCTCT TCAAATTCTG	11400

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FIGURE 12J

ACAGATATTT	CTGGCATATT	TCTGAAGGTG	CTTTCTTGGC	CATCTCCTTC	11450
ACAGTGTAC	TCAGATAGTT	GAAGCCATTT	TGTTGCTCTT	TCAAAGAACT	11500
TTGCAGAGCC	TGTAATTTCC	CGAGTCTCTC	CTCCATTATT	TCATATTCAG	11550
TAACTAAG	ATAAGGTACA	GAGAGTTTGC	TTTCTGACTG	CTGGATCCAC	11600
GTCCTGATGC	TACTCATTGT	CTCCTGATAG	CGCATTGGTG	GTAAAGTGTC	11650
AAAAATTGTC	TGTAGCTCTT	TCTCTTTGGC	CCTCACACCA	TCAAAGATGT	11700
GGTTAAATG	ATTAGTAAAG	GCCACAAAGT	CTGCATCCAG	AAACATTGGC	11750
CCCTGTCCTT	TTTCTTTCAG	TTGTAGACTC	TGAATTTTTTA	ATTGCTCAAT	11800
TTGAGGCTGA	AGAGCTGACA	ATCTGTTGAC	TTCATCCTTA	CAAATTTTTTA	11850
ACTGGCTTTT	AATTGCTGTT	GGCTCTGATA	GGGTGGTAGA	CTGGGTTTTTC	11900
AACAAGTTTT	CGGCAGTAGT	TGTCATCTGT	TCCAATTGTT	GTAGCTGATT	11950
ATAAAAGGTA	ATGATGTTGG	TTTGATACTC	TAGCCAGTTA	ACTCTCTCAC	12000
TCAGCAATTG	GCAGAATTCT	GTCCACCGGC	TGTTCAAGTTG	TTCTGAAGCT	12050
TGTCTGATAC	TTTCAGCATT	AACACCCTCA	TTTGCCATCT	GTTCCACCAG	12100
GGCCTGAGCT	GATCTGCTGG	CATCTTGCAG	TTTTCTGAAC	TTCTCTGCTT	12150
TTTCTCGTGC	TATGGCATTG	ACTTTTTCTT	GCAAGTCTGA	GATGTTGCCT	12200
TCTTTTCGAT	AGACTGCAAA	TTCAGAACTC	TGTAATACAG	CTTCTGAACG	12250
AGTAATCCAA	CTGTGAAGTT	CAGTTATATC	GACATCCAAC	CTTTTCCTGA	12300
G TTCAGAATC	CACAGTTATC	TGCCTCTTCT	TTTGAGGAGG	TGGTGGTGGA	12350
AGTTCCTCTT	GGGCATGTTT	TACCATGATT	TGTTCCCTTG	TGGTCACCAT	12400
AGTTACCGTT	TCCATTACAG	TTGTCTGTGT	TAGGGATGGT	TGAGTGGTGG	12450
TGACAGCCTG	TGAAATTTGT	GCTGAACTCT	TTTCAAGTTT	TTGGGTAAAA	12500
TTGTCCCAAC	GTTGTGCAAA	GTTTTCCATC	CAGATTTCCA	TCTTTTGAGT	12550
CACTGACTTA	TTTTTCAGTG	CCGAAAGTAG	ATCTTGATTG	AGTGAACCTA	12600
GTTTTTCAT	GGTTGGCTTT	TTCTTTTCTA	GATCTATTTT	TAAAGTAGAT	12650

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FIGURE 12K

ATTTTGTGAA GACTTGACAT CATTTCAATTT TGATCTTTAA AGCCACTTGT	12700
CTGAATGTTT TTCATTGCAT CTTCTTTTTC TGAAAGCCAT GACTAAAAA	12750
GGCACTGTTT TTCAGTAAAA TGCTGCCATT TTAGAAGAAT ATCTTGTA	12800
ACAATCCAGC GGTCTTCAGT CCATCTGCAG ATATTTGCCC ATCGATCTCC	12850
CAGTACCTTA AGTTGTTCTT CCAAAGCAGC TGTTGCATGA TCACCGCTGG	12900
ATTCATCAAC CACTACTACC ATGTGAGTGA GCGAGTTGAC CCTGACCTGC	12950
TCCTGTTCTA GATCTTCTTG AAGCACCTTA TGTTGTTGTA CTTGGCATTT	13000
TAGATCTTCA AGATCAGGTC CAAAGGGCTC TTCCTCCATT TTCTTAGTTC	13050
TCTCTTCAGT TTTTGTAAAC CAGTCATCTA GTTCTTTTAA TTTCTGATTC	13100
TGGAGATCCA TTAGAACTTT GTGTAATTTG CTTTGTTTTT CCATGCTAGC	13150
TACCCTGAGA CATTCCCATC TTGAATTTAG GAGATTCATT TGTTCTTGCA	13200
CTTCAGCTTC TTCATCTTCT GATAATTTCC CTTTTCCAAC TAGTTGACTT	13250
CCTAACTGTA GAACATTACC AACAAAGTCCT TGATGAGATG TCAGATCCAT	13300
CATGAATCCC TCATGAGCAT GAAACTGTTT TTTCACTTCT TCAACATCAT	13350
TTGAAATCTC TCCTTGCTGT CGCAATGTAT CCTCGGCAGA AAGAAGCCAT	13400
GAAAGTACTT CTTCTAAAGC AGTTTGGTAA CTATCCAGAT TTAATTCGGT	13450
CTCCATCAAT GAACTGTCAA GTGACTTGTC TCTGGGAGCT TCCAAATGCT	13500
GTGAAGGATA GGGGCTCTGT GTGGAATCAG AGGTGGCAAC ATAAGCAGCC	13550
TGTGTGAAGG CATAACTCTT GAATCGAGGC TTAGGAGATG AAGAAGTTTG	13600
TTCATAGCCC TGTGCTAGAC TGAATGTGAT CTGTTGAGAG TAATGCATCT	13650
GGTGATGTAA TTGAAAATGT TCTTCTCTAG TTAATTTTGA AGATGTCCTG	13700
GGCAACATTT CCACTTCTTG AATGGCTTCA ATGCTCACTT GTTGTGGCAA	13750
AACCTGAAAG AGTGATGTGA TGTACATTAA GATGGACTTC TTGTCTGGAT	13800
AAGTGGTAGC AACATCTTCA GGATCAAGAA GTTTTTCTAT GCCTAACTGG	13850
CATTTTGCAA TGTTGAAGGC ATGTTCCAGT CTTTGGGTGG CTGAGTGCTG	13900

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FIGURE 12L

TGAAACCACA	CTATTCCAAT	CAAACAGGTC	GGGCCTGTGA	CTATGGATAA	13950
GAGCATTCAA	AGCCAACCCG	TCGGACCAGC	TAGAGGTGAA	GTTGATGACG	14000
TTAACCTGTG	GATAATTACG	TGTTGACTGT	CGAACCCAGC	TCAGAAGAAT	14050
CTTTTCACTG	TTGGTTTGCT	GCAATCCAGC	CTGATAGTT	TTCATCACAT	14100
TTTTGACCTG	CCAGTGGAGG	ATTATATTCC	AAATCAAACC	AAGAGTGAGT	14150
TTATGATTTC	CATCCACTAT	GTCAGTGCTT	CCTATATTCA	CTAAATCAAC	14200
ATTATTTTTC	TGTAAGACCC	GCAGTGCCTT	GTTGACATTG	TTCAGGGCAT	14250
GAACTCTTGT	AGATCCCTTT	TCTTTTGGCA	GTTTTTGCCC	TGTAAGGCCT	14300
TCCAAGAGGT	CTAGGAGGCG	TTTTCCATCC	TGCAGGTCAC	TGAAGAGGTT	14350
GTCTATGTGT	TGCTTTCCAA	ACTTAGAAAA	TTGTGCATTT	ATCCATTTTG	14400
TGAATGTTTT	CTTTTGAACA	TCTTCTCTTT	CATAACAGTC	CTCTACTTCT	14450
TCCCACCAAA	GCATTTGGAA	GAAAAAGTAT	ATATCAAGGC	AGGGATAAAA	14500
ATCTTGGTAA	AAGTTTCTCC	CAGTTTATT	GCTCCAGGAG	GCTTAGGTAC	14550
GATGAGAAGC	CAATAAACTT	CAGCAGCCTT	GACAAAAAAA	AAAAAAAAAA	14600
TAGCACTTCA	AGTCTTCCTA	TCGTTTTTTT	CTATAAAGCT	ATTGCCTTCA	14650
AGAGCGGAAT	TCCTGCAGCC	CGGGGGATCC	ACTAGTTCTA	GAGCGGCCGC	14700
GGGTACAATT	CCGCAGCTTT	TAGAGCAGAA	GTAACACTTC	CGTACAGGCC	14750
TAGAAGTAAA	GGCAACATCC	ACTGAGGAGC	AGTTCTTTGA	TTTGCACCAC	14800
CACCGGATCC	GGGACCTGAA	ATAAAAGACA	AAAAGACTAA	ACTTACCAGT	14850
TAACTTTCTG	GTTTTTCAGT	TCCTCGAGTA	CCGGATCCTC	TAGAGTCCGG	14900
AGGCTGGATC	GGTCCCGGTG	TCTTCTATGG	AGGTCAAAC	AGCGTGGATG	14950
GCGTCTCCAG	GCGATCTGAC	GGTTCATAA	ACGAGCTCTG	CTTATATAGA	15000
CCTCCCACCG	TACACGCCTA	CCGCCCATTT	GCGTCAATGG	GGCGGAGTTG	15050
TTACGACATT	TTGGAAAGTC	CCGTTGATTT	TGGTGCCAAA	ACAAACTCCC	15100
ATTGACGTCA	ATGGGGTGGA	GACTTGGAAA	TCCCCGTGAG	TCAAACCGCT	15150
ATCCACGCCC	ATTGATGTAC	TGCCAAAACC	GCATCACCAT	GGTAATAGCG	15200

FIGURE 12M

ATGACTAATA CGTAGATGTA CTGCCAAGTA GGAAAGTCCC ATAAGGTCAT	15250
GTACTGGGCA TAATGCCAGG CGGGCCATTT ACCGTCATTG ACGTCAATAG	15300
GGGGCGTACT TGGCATATGA TACACTTGAT GTACTGCCAA GTGGGCAGTT	15350
TACCGTAAAT ACTCCACCCA TTGACGTCAA TGGAAAGTCC CTATTGGCGT	15400
TACTATGGGA ACATACGTCA TTATTGACGT CAATGGGCGG GGGTCGTTGG	15450
GCGGTCAGCC AGGCGGGCCA TTTACCGTAA GTTATGTAAC GACCTGCAGG	15500
TCGACTCTAG AGGATCTCCC TAGACAAATA TTACGCGCTA TGAGTAACAC	15550
AAAATTATTC AGATTTCACT TCCTCTTATT CAGTTTTCCC GCGAAAATGG	15600
CCAAATCTTA CTCGGTTACG CCCAAATTTA CTACAACATC CGCCTAAAAC	15650
CGCGCGAAAA TTGTCACTTC CTGTGTACAC CGGCGCACAC CAAAAACGTC	15700
ACTTTTGCCA CATCCGTCGC TTACATGTGT TCCGCCACAC TTGCAACATC	15750
ACACTTCCGC CACACTACTA CGTCACCCGC CCCGTTCCCA CGCCCCGCGC	15800
CACGTCACAA ACTCCACCCC CTCATTATCA TATTGGCTTC AATCCAAAAT	15850
AAGGTATATT ATTGATGATG CTAGCGGGGC CCTATATATG GATCCAATTG	15900
CAATGATCAT CATGACAGAT CTGCGCGCGA TCGATATCAG CGCTTTAAAT	15950
TTGCGCATGC TAGCTATAGT TCTAGAGGTA CCGGTTGTTA ACGTTAGCCG	16000
GCTACGTATA CTCCGGAATA TTAATAGGCC TAGGATGCAT ATGGCGGCCG	16050
GCCGCCTGCA GCTGGCGCCA TCGATACGCG TACGTCGCGA CCGCGGACAT	16100
GTACAGAGCT CGAGAAGTAC TAGTGGCCAC GTGGGCCGTG CACCTTAAGC	16150
TTGGCACTGG CCGTCGTTTT ACAACGTCGT GACTGGGAAA ACCCTGGCGT	16200
TACCCAACTT AATCGCCTTG CAGCACATCC CCCTTTCGCC AGCTGGCGTA	16250
ATAGCGAAGA GGCCCGCACC GATCGCCCTT CCCAACAGTT GCGCAGCCTG	16300
AATGGCGAAT GGCGCCTGAT GCGGTATTTT CTCCTTACGC ATCTGTGCGG	16350
TATTTACACAC CGCATACGTC AAAGCAACCA TAGTACGCGC CCTGTAGCGG	16400
CGCATTAAAGC GCGGCGGGTG TGGTGGTTAC GCGCAGCGTG ACCGCTACAC	16450

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FIGURE 12N

TTGCCAGCGC	CCTAGCGCCC	GCTCCTTTTCG	CTTTCTTCCC	TTCCTTTCTC	16500
GCCACGTTTCG	CCGGCTTTCC	CCGTCAAGCT	CTAAATCGGG	GGCTCCCTTT	16550
AGGGTTCCGA	TTTAGTGCTT	TACGGCACCT	CGACCCCAA	AACTTGATT	16600
TGGGTGATGG	TTCACGTAGT	GGGCCATCGC	CCTGATAGAC	GGTTTTTCGC	16650
CCTTTGACGT	TGGAGTCCAC	GTTCTTTAAT	AGTGGACTCT	TGTTCCAAAC	16700
TGGAACAACA	CTCAACCCTA	TCTCGGGCTA	TTCTTTTGAT	TTATAAGGGA	16750
TTTTGCCGAT	TTCGGCCTAT	TGGTTAAAA	ATGAGCTGAT	TTAACAAAA	16800
TTTAACGCGA	ATTTTAACAA	AATATTAACG	TTTACAATTT	TATGGTGCAC	16850
TCTCAGTACA	ATCTGCTCTG	ATGCCGCATA	GTTAAGCCAG	CCCCGACACC	16900
CGCCAACACC	CGCTGACGCG	CCCTGACGGG	CTTGTCTGCT	CCCGGCATCC	16950
GCTTACAGAC	AAGCTGTGAC	CGTCTCCGGG	AGCTGCATGT	GTCAGAGGTT	17000
TTCACCGTCA	TCACCGAAAC	GCGCGAGACG	AAAGGGCCTC	GTGATACGCC	17050
TATTTTTATA	GGTTAATGTC	ATGATAATAA	TGGTTTCTTA	GACGTCAGGT	17100
GGCACTTTTC	GGGGAAATGT	GCGCGGAACC	CCTATTTGTT	TATTTTTCTA	17150
AATACATTCA	AATATGTATC	CGCTCATGAG	ACAATAACCC	TGATAAATGC	17200
TTCAATAATA	TTGAAAAGG	AAGAGTATGA	GTATTCAACA	TTTCCGTGTC	17250
GCCCTTATTC	CCTTTTTTGC	GGCATTTTGC	CTTCTGTGTT	TTGCTCACCC	17300
AGAAACGCTG	GTGAAAGTAA	AAGATGCTGA	AGATCAGTTG	GGTGCACGAG	17350
TGGGTTACAT	CGAACTGGAT	CTCAACAGCG	GTAAGATCCT	TGAGAGTTTT	17400
CGCCCCGAAG	AACGTTTTCC	AATGATGAGC	ACTTTTAAAG	TTCTGCTATG	17450
TGGCGCGGTA	TTATCCCGTA	TTGACGCCGG	GCAAGAGCAA	CTCGGTCGCC	17500
GCATACACTA	TTCTCAGAAT	GACTTG GTT	AGTACTCACC	AGTCACAGAA	17550
AAGCATCTTA	CGGATGGCAT	GACAGTAAGA	GAATTATGCA	GTGCTGCCAT	17600
AACCATGAGT	GATAACACTG	CGGCCAACTT	ACTTCTGACA	ACGATCGGAG	17650
GACCGAAGGA	GCTAACCCT	TTTTTGCACA	ACATGGGGGA	TCATGTAAC	17700

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FIGURE 120

CGCCTTGATC GTTGGGAACC GGAGCTGAAT GAAGCCATAC CAAACGACGA	17750
GCGTGACACC ACGATGCCTG TAGCAATGGC AACAACTTG CGCAAATAT	17800
TAAGTGGCGA ACTACTTACT CTAGCTTCCC GGCAACAATT AATAGACTGG	17850
ATGGAGGCGG ATAAAGTTGC AGGACCACTT CTGCGCTCGG CCCTTCCGGC	17900
TGGCTGGTTT ATTGCTGATA AATCTGGAGC CGGTGAGCGT GGGTCTCGCG	17950
GTATCATTGC AGCACTGGGG CCAGATGGTA AGCCCTCCCG TATCGTAGTT	18000
ATCTACACGA CGGGGAGTCA GGCAACTATG GATGAACGAA ATAGACAGAT	18050
CGCTGAGATA GGTGCCTCAC TGATTAAGCA TTGGTAACTG TCAGACCAAG	18100
TTTACTCATA TATACTTTAG ATTGATTAA AACTTCATTT TTAATTTAAA	18150
AGGATCTAGG TGAAGATCCT TTTTGATAAT CTCATGACCA AAATCCCTTA	18200
ACGTGAGTTT TCGTTCCACT GAGCGTCAGA CCCCCTAGAA AAGATCAAAG	18250
GATCTTCTTG AGATCCTTTT TTTCTGCGCG TAATCTGCTG CTTGCAAACA	18300
AAAAAACCAC CGCTACCAGC GGTGGTTTGT TTGCCGGATC AAGAGCTACC	18350
AACTCTTTTT CCGAAGGTAA CTGGCTTCAG CAGAGCGCAG ATACCAAATA	18400
CTGTTCTTCT AGTGTAGCCG TAGTTAGGCC ACCACTTCAA GAACTCTGTA	18450
GCACCGCCTA CATACCTCGC TCTGCTAATC CTGTTACCAG TGGCTGCTGC	18500
CAGTGGCGAT AAGTCGTGTC TTACCGGGTT GGAATCAAGA CGATAGTTAC	18550
CGGATAAGGC GCAGCGGTCTG GGCTGAACGG GGGGTTCGTG CACACAGCCC	18600
AGCTTGGAGC GAACGACCTA CACCGAAGT AGATACCTAC AGCGTGAGCT	18650
ATGAGAAAGC GCCACGCTTC CCGAAGGGAG AAAGGCGGAC AGGTATCCGG	18700
TAAGCGGCAG GGTGGAACA GGAGAGCGCA CGAGGGAGCT TCCAGGGGGA	18750
AACGCCTGGT ATCTTTATAG TCCTGTCGGG TTTCGCCACC TCTGACTTGA	18800
GCGTCGATTT TTGTGATGCT CGTCAGGGGG GCGGAGCCTA TGGAAAAACG	18850
CCAGCAACGC GGCCTTTTAA CGGTTCTTGG CCTTTTGCTG GCCTTTTGCT	18900
CACATGTTCT TTCCTGCGTT ATCCCCTGAT TCTGTGGATA ACCGTATTAC	18950

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FIGURE 12P

CGCCTTTGAG	TGAGCTGATA	CCGCTCGCCG	CAGCCGAACG	ACCGAGCGCA	19000
GCGAGTCAGT	GAGCGAGGAA	GCGGAAGAGC	GCCCAATACG	CAAACCGCCT	19050
CTCCCCGCGC	GTTGGCCGAT	TCATTAATGC	AGCTGGCACG	ACAGGTTTCC	19100
CGACTGGAAA	GCGGGCAGTG	AGCGCAACGC	AATTAATGTG	AGTTAGCTCA	19150
CTCATTAGGC	ACCCCAGGCT	TTACACTTTA	TGCTTCCGGC	TCGTATGTTG	19200
TGTGGAATTG	TGAGCGGATA	ACAATTTTAC	ACAGGAAACA	GCTATGACCA	19250
TGATTACGAA	TTCGAATGGC	CATGGGACGT	CGACCTGAGG	TAATTATAAC	19300
CCGGGCC					19307

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